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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR TOBACCO PRODUCTS

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TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

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M E E T I N G

(8:30 a.m.)

DR. MERMELSTEIN: Good morning, we're going to get started, if people want to take seats. I'm Robin Mermelstein, I am the Chair of the Tobacco Products Scientific Advisory Committee, so thank you all for joining us and braving the threats of the weather, so we're glad that everyone is here to participate in the meeting. I have a few statements to make and then we're going to go around and introduce the Committee.

For topics such as those discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goals at today's meeting will be a fair and open forum for discussion of these issues and individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by me, as Chair, so we're looking forward to having a productive meeting and a fair and open one.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topics at hand take place in the open forum of the meeting.

We are aware that members of the media may be anxious to

speak with the FDA about the proceedings; however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the Committee is reminded to please refrain from discussing the meeting topics during the breaks. Lots of other things to talk about, so thank you all.

Caryn?

MS. COHEN: The Center for Tobacco Products of the Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the Authority of the Federal Advisory Committee Act of 1972 and the Family Smoking and Prevention and Tobacco Control Act of 2009.

The Committee is composed of scientists, healthcare professionals, a representative of a state government, a representative of the general public, ex-officio participants from other agencies, and three industry representatives. With the exception of the industry representatives, all Committee members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with applicable federal conflict of

interest law and regulations is being provided to participants in today's meeting and to the public.

The purpose of today's meeting is to discuss modified risk tobacco product applications submitted by R.J. Reynolds Tobacco Company for six products. They are Camel Snus Frost, Camel Snus Frost Large, Camel Snus Mellow, Camel Snus Mint, Camel Snus Robust, and Camel Snus Winterchill.

Accordingly, this meeting is categorized as one involving a particular matter involving specific parties.

Based on the categorization of the meeting and the matters to be considered by the Committee, all meeting participants, with the exception of the three industry representatives, have been screened for potential conflicts of interest. FDA has determined that the screened participants are in compliance with applicable federal conflict of interest laws and regulations.

With respect to the Committee's industry representatives, we would like to disclose that Drs. William Andy Bailey, Willie McKinney, and David Johnson are participating in this meeting as non-voting representatives. Dr. Bailey is acting on behalf of the interests of the tobacco growers; Dr. McKinney is acting on behalf of the interests of the tobacco manufacturing

industry; and Dr. Johnson is acting on behalf of the interests of small business tobacco manufacturing industry.

Their role at this meeting is to represent these industries in general and not any particular company. Dr. Bailey is employed by the University of Kentucky, Dr. McKinney is employed by Altria Client Services, and Dr. Johnson is employed by National Tobacco Company.

Thank you.

DR. MERMELSTEIN: Thank you, Caryn.

We're going to go around and have committee introductions. I'll start, and I am Robin Mermelstein. I am a professor at the University of Illinois at Chicago.

Dr. Duffy.

DR. DUFFY: Sonia Duffy, Ohio State University, professor.

DR. WEITZMAN: Hi, I'm Michael Weitzman. I'm a professor at New York University School of Medicine.

DR. BIERUT: My name is Laura Bierut. I'm a Professor of Psychiatry at Washington University in St. Louis.

DR. BLAHA: Hi. Michael Blaha, Director of Clinical Research, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease.

DR. WACKOWSKI: Hi. Olivia Wackowski, assistant professor

at the Rutgers School of Public Health.

DR. KITTNER: Good morning, I'm Deirdre Lawrence Kittner, I'm a technical project lead, and I'm also the Deputy Director in the Division of Population Health Science here at FDA.

DR. HOLMAN: Good morning. Matt Holman, Director of the Office of Science at FDA's Center for Tobacco Products.

MR. ZELLER: Good morning. Mitch Zeller, Director, Center for Tobacco Products.

DR. McKINNEY: Good morning. Willie McKinney. I'm the Vice President of Regulatory Sciences at Altria Client Services, and I serve as the Industry Representative.

DR. JOHNSON: Good morning. I'm David Johnson, and I work for National Tobacco Company, and I'm representing the interests of the small tobacco manufacturers.

DR. BAILEY: Andy Bailey, the University of Kentucky, dark tobacco extension specialist, here to represent tobacco growers.

MS. BECENTI: Good morning, I'm Alberta Becenti with the Indian Health Service.

DR. KING: Good morning, I am Brian King with the U.S. Centers for Disease Control and Prevention, Office on Smoking and Health.

DR. WANKE: I'm Kay Wanke with the -- I'm the Deputy Director of the Tobacco Regulatory Science Program in the Office of Disease Prevention at the National Institutes of Health.

DR. OSSIP: And good morning. I'm Deborah Ossip. I'm a professor at the University of Rochester Medical Center.

DR. MERMELSTEIN: We also have a couple of Committee members who will be joining us on the phone.

Dr. Herndon, are you there?

MS. HERNDON: Hello, this is Sally Herndon. I'm head of the Tobacco Prevention and Control Branch for the Division of Public Health in North Carolina, and I represent the state government thought on this Committee. Thank you for letting me call in.

DR. MERMELSTEIN: And Dr. Thrasher?

DR. THRASHER: Yeah, hi. Jim Thrasher, professor in the Arnold School of Public Health, the University of South Carolina.

DR. MERMELSTEIN: Great. Thank you, Jim and Sally. Appreciate your participating even during the trying time, and hopefully Dr. Giovino will be joining us as well.

DR. GIOVINO: Oh, I'm here.

DR. MERMELSTEIN: Gary, you want to introduce yourself?

DR. GIOVINO: I'm sorry. Gary Giovino at the University of Buffalo, professor and department chair.

DR. MERMELSTEIN: Great, thank you.

Dr. Holman.

DR. HOLMAN: Good morning. On behalf of FDA and CTP, I just want to say welcome to all the attendees, both in the room as well as those participating via the web. Today and tomorrow the Committee will hear evidence and participate in an in-depth discussion about modified risk --

DR. KOZLOWSKI: Excuse me, there's one more. Hi, this is Lynn Kozlowski at the University of Buffalo. Can you hear me?

DR. MERMELSTEIN: Yes. Thank you very much, Dr. Kozlowski. And --

DR. TOMAR: Yeah, hi. This is Scott Tomar, professor at the University of Florida.

DR. MERMELSTEIN: Great. Thank you, both. Appreciate your joining us.

DR. HOLMAN: As I was saying, today and tomorrow the Committee will hear evidence and participate in an in-depth discussion about modified risk tobacco product applications submitted by R.J. Reynolds Tobacco Company for six Camel Snus

products.

The Federal Food, Drug, and Cosmetic Act outlines requirements that must be met before FDA can authorize marketing of a modified risk tobacco product. We must ensure that the modified risk claims are substantiated and supported by scientific evidence. We also have a legal and ethical obligation to make sure the public is not misled about the relative risks of a tobacco product.

That means that the applicant must demonstrate that a proposed modified risk tobacco product, as actually used by consumers, will significantly reduce risk to individual users of the product as well as benefit the population as a whole. Therefore, FDA must consider the likelihood that users who would have otherwise quit tobacco completely instead switch to a modified risk tobacco product or use a modified risk tobacco product with another tobacco product.

FDA must also consider the likelihood that nonusers will initiate tobacco use with a modified risk tobacco product, and here, we're especially concerned about youth use or initiation.

So, lastly, I just want to say thank you to the Committee. Your task over the next 2 days is to provide FDA with your assessment and recommendations on the matters brought before

you. I want to thank you for your preparation ahead of the meeting as well as your efforts over the next 2 days.

I also want to give thanks to Dr. Mermelstein. She's provided expertise on this Committee for over 2 years. This is her first meeting chairing on the Committee, and I really appreciate her willingness to accept that role and responsibility.

And, lastly, thank you to all the other participants, again, both in the room as well as those over the web, and special thanks to those participating in the open public hearing tomorrow.

So with that, I'll turn it over to Dr. Kittner.

DR. KITTNER: Good morning, everyone. My name is Dr. Deirdre Lawrence Kittner, and I am the Deputy Director in the Division of Population Health Science. Do I need to start the slides?

(Pause.)

DR. KITTNER: My name is Dr. Deirdre Lawrence Kittner, and I am the Deputy Director of the Division of Population Health Science in CTP's Office of Science. I'm going to present an overview of the modified risk tobacco product application process and the applications currently under review at FDA from

RJR Reynolds, R.J. Reynolds Tobacco Company.

First, I will start with a disclaimer. Just to let you know, this disclaimer is relevant to all FDA presentations. All FDA presenters have this in their slides, but I will be the only one to read it.

The information in these materials does not represent Agency position or policy. The information is being provided to TPSAC to aid in its evaluation of the issues and questions referred to the Committee.

This presentation contains information prepared by the FDA for the members of the TPSAC. The presentation describes assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the review division or office.

This presentation may not include all of the issues relevant to FDA's decision on the applications and instead is intended to focus on issues identified by FDA for discussion by TPSAC. The FDA will not make its determination on the issues at hand until input from TPSAC and from the public comments have been considered and all FDA reviews have been finalized.

FDA's determination may be affected by issues not discussed at the TPSAC meeting.

This is a brief outline of what I will be discussing. I will first start with a high-level overview of the statutory framework for modified risk tobacco products and the FDA review process. I will then provide a brief summary of RJRT applications under review, and finally, a summary of the questions that we were asking the Committee to answer during this 2-day meeting. Thank you.

Section 911 of the Federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act, defines a modified risk tobacco product (MRTP) as a tobacco product sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products.

This includes products whose label, labeling, or advertising represents, explicitly or implicitly, that the product is less harmful or represents a lower risk of tobacco-related disease than other commercially marketed tobacco products; the tobacco or its smoke contains a reduced level of, presents a reduced exposure to, or does not contain/is free of a substance. This also includes products which use the

descriptors light, mild, or low, or similar descriptors.

In a moment, I will talk about the standards for authorization of modified risk tobacco products as laid out in the statute. But, first, I want to provide a little more context for the MRTP pathway.

Before an MRTP can be introduced or delivered for introduction into interstate commerce, an order from FDA under Section 911(g) of the FD&C Act must be in effect with respect to the tobacco product. An MRTP order is an order for a specific product with modified risk labels, labeling, or advertising.

To legally sell an MRTP that is also a new tobacco product, a company must have authorization from FDA under Section 911(e), an MRTP order, and the product must comply with the premarket requirements of Section 910.

Just as a reminder, the MRTP is not a pathway to market a product. RJRT submitted provisional SE reports in premarket tobacco product applications. This meeting is focused on the MRTPAs. TPSAC is not here to determine whether the products, without modified risk information, satisfy the applicable standards for premarket review. This is about being able to market these six products with the specific modified risk

information proposed.

Under 911(g)(1), in determining whether modified risk orders should be issued, FDA must assess whether it has been demonstrated that the product, as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. We call this a risk modification order.

Section 911(g)(2) of the FD&C Act describes a special rule for certain products which allows FDA to issue an order, an exposure modification order, for products that cannot receive a risk modification order under Section 911(g)(1).

If it determines that the applicant has demonstrated, among other things, some of the parameters listed here, such as the order would be appropriate to promote the public health, and the scientific evidence that is available demonstrates that a measurable and substantial reduction in morbidity and mortality among individual tobacco users is reasonably likely in subsequent studies. The others are listed here.

The evaluation of an MRTPA can be thought of in terms of a few key overarching questions. Each of these steps involves

the evaluation of many specific questions which draws from multiple scientific disciplines. In evaluating an MRTPA, CTP has to consider the product with the proposed modified risk information. The questions include:

- Is there adequate scientific substantiation of the proposed modified risk information?
- What are the health risks of the MRTP to individual tobacco users?
- How do consumers perceive and understand the modified risk information? And
- What are the potential benefits and harms to the health of the population as a whole?

This figure represents a summary of the MRTPA review process. Often, potential applicants will request a meeting with the Agency to discuss the potential application. That is described here as Phase Zero.

When FDA receives an application, an acceptance review is conducted to ensure that it meets certain basic requirements, such as being legible and in English.

The next step is a filing review to ensure that the application includes the required information as described in the statute.

Once filed, the application undergoes a substantive scientific review and in the case of MRTPAs, a referral to the TPSAC as well as the posting of the applications redacted in accordance with applicable laws for public comment.

After complete review, FDA will take action on the application. If an order is granted, the applicant would conduct required postmarket surveillance studies. MRTP orders are time limited; therefore, a renewal will be needed to continue marketing a product as modified risk.

Now on to the applications under review and the focus of this TPSAC meeting.

FDA received MRTPAs from RJRT which state that RJRT is seeking orders, under Section 911(g)(1), for six Camel Snus products: Camel Snus Frost, Frost Large, Winterchill, Robust, Mellow, and Mint.

The Applicant describes its six Camel Snus products as portioned pouched products that use a blend of heat-treated flavored tobaccos, are pouched in a porous fleece material, and are packaged in metal tins. Each metal tin contains 15 pouches.

The Applicant states that the product is intended to be placed under the lip and there is typically no expectoration or

spitting. The consumer disposes of the pouch when he or she is finished using the product.

As I previously described under 911(g)(1) or risk modification order, FDA must assess whether it has been demonstrated that the product, as it's actually used by the consumer, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both the users of tobacco products and persons who do not currently use tobacco products.

The Agency is making the applications, redacted in accordance with applicable laws, publicly available on a rolling basis. Once all materials from these MRTPAs, including amendments, are posted, FDA will announce the closing date for the comment period which will be at least 30 days from the date the last application materials are posted.

RJRT submitted three different advertising executions for each of the six Camel Snus products under review. The Applicant differentiated the ad executions based on what it referred to as the following key modified risk claims:

- Smokers who switch completely from cigarettes to Camel Snus can significantly reduce their risk of

lung cancer, oral cancer, respiratory disease, and heart disease.

- Smokers who switch completely from cigarettes to Camel Snus can greatly reduce their risk of lung cancer, oral cancer, and respiratory disease and heart disease.
- Smokers who switch completely from cigarettes to Camel Snus can greatly reduce the risk of lung cancer and respiratory disease.

As part of its evaluation of the MRTPAs, FDA is reviewing modified risk information identified across the three advertising executions submitted by the Applicant. Modified risk information is bolded. For example, as you see on the left side of this slide, scientific studies have shown that Camel Snus contains fewer carcinogens than cigarette smoke. And on the right side of the slide, no smoke means fewer carcinogens and no smoke equals less risk.

FDA is reviewing the scientific information submitted in the MRTPAs to determine whether the statutory requirements for authorization provided in Section 911 of the FD&C Act have been met. In addition to the evidence presented by the Applicant, we will consider recommendations made today, public comments,

and any other scientific evidence or information that is available to the Agency. We evaluate scientific substantiation of the proposed modified risk information, health risks of the MRTP to individual tobacco users, consumer understanding and perception of the modified risk information, and the potential benefits and harms to the health of the population as a whole.

This graphic is a rough representation of the multiple lines of evidence under consideration. Today we are specifically asking the Committee to focus on three areas:

- evidence related to the substantiation of the modified risk information;
- consumer perception and understanding; and
- likelihood of use of the proposed MRTPAs.

First, we will ask you to focus on assessing the evidence related to the health risks of the proposed MRTPs and substantiation of the modified risk information.

This is what we will ask you to spend most of your time discussing: The proposed advertising submitted in MRTPAs contains multiple modified risk statements. The modified risk information is primarily centered around reduction of harmful constituents and reduced disease risk.

FDA's Dr. Mimy Young will present the product chemistry,

nonclinical and clinical studies. She will be followed by Ms. Catherine Corey, who will present the epidemiological evidence used to assess the scientific accuracy of the statements. TPSAC will be asked to discuss the evidence and the substantiation, i.e., the scientific accuracy of these statements.

Next, we will ask you to consider consumer perceptions and understanding of the modified risk information which will be presented by Dr. Erin O'Brien. The Applicant submitted several versions of three-page print advertisements for the six Camel Snus products which include modified risk information. She will present the ads along with results from RJRT's online studies that were conducted to test consumer understanding and perceptions of the modified risk information in the ads. We will ask TPSAC to discuss potential applications of the language in the ads on consumer understanding and perceptions.

Finally, we will ask you to discuss the likelihood of use of the proposed MRTPs. Dr. O'Brien will present data from several observational studies to describe characteristics of Camel Snus users, patterns of use, and transitions from cigarette smoking to snus use.

In addition, FDA will present the likelihood of use

studies conducted by the Applicant to assess the likelihood that cigarette smokers will switch to the six Camel Snus products when presented with modified risk information. TPSAC will be asked to discuss the potential use behaviors with respect to the proposed modified risk products.

Here are the questions that we're posing to TPSAC. And while evaluating your responses to the questions, please keep the 911(g)(1) standard in mind because, as I described earlier, the Applicant submitted MRTPAs seeking orders under Section 911(g)(1) of the FD&C Act for Camel Snus products. That is, the Agency must find that the products, as actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and those who do not currently use tobacco products.

The modified risk information in the ad executions include RJRT's key claims about the reduction in disease risk as a result of completely switching from cigarettes. So Question 1 specifically asks you to evaluate the evidence related to the reduced disease risk, discuss the available scientific evidence and vote on the extent to which the available scientific

evidence substantiates the following modified risk information in the Applicant's advertising: Smokers who switch completely from cigarette to Camel Snus can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, heart disease.

Question 2: The applicant's advertising also contains modified risk information that describes a reduction in harmful constituents in Camel Snus versus cigarettes, and modified risk information that is not as specific as the information presented in Question 1, for example, does not reference reduction in specific diseases or the need for complete switching.

All of these statements are being evaluated as part of the MRTPAs. We are asking the Committee to discuss the available scientific evidence and vote on the extent to which the available scientific evidence substantiates the following modified risk information in the advertising:

a. Camel SNUS contains less of the harmful chemicals than cigarettes.

b. Smokers who use Camel SNUS instead of cigarettes can significantly reduce their health risks from smoking.

c. Switching to snus means less risk for you.

d. No smoke equals less risk.

Question 3: In addition to evaluating the proposed modified risk information for scientific accuracy, FDA also evaluates consumer understanding and perceptions of the modified risk information in the advertising.

The Applicant plans to communicate all of the information together; that is, the first page has less specific information while the second and third pages have more specific modified risk information and additional information that RJRT refers to as balancing information, for example, that Camel Snus and other tobacco products contain nicotine and are addictive, and the recommendation that smokers concerned about the health risks of smoking should quit and talk to a healthcare provider.

We are asking the Committee to discuss the potential implications of modified risk information, including non-specific modified risk information, as described in Question 2, on consumer understanding and perceptions. Specifically, we would like to hear the Committee consider the questions, such as:

a. Can the non-specific modified risk information be misinterpreted?

b. Is there sufficient evidence that consumers would

understand the non-specific modified risk information?

c. Is there sufficient evidence about the impact of the non-specific modified risk information on the likelihood of use?

d. Is there sufficient evidence about the impact of the non-specific modified risk information on poly tobacco use or partial switching?

The final question will provide an opportunity to discuss the potential users of the six proposed Camel Snus MRTPs.

a. What is the likelihood that cigarette smokers will switch completely to the six Camel Snus products?

b. Are there other groups of potential users, particularly unintended users, for example, youth or former cigarette smokers, of concern?

We look forward to hearing your thoughtful comments.

DR. MERMELSTEIN: Thank you.

Any questions from the Committee to Dr. Lawrence?

Dr. Weitzman.

DR. WEITZMAN: So I saw only in the last slide any mention of unintended users, youth, so are youths not central to the consideration of many of the other questions? And unless I

missed it, the comparisons in terms of toxicology or potential risk have to do with the relationship to cigarettes or combusted tobacco and I didn't see other types of snus. Am I missing that, or is that correct?

DR. KITTNER: Excuse me, you're right, that is -- the question will be evaluating everything within FDA in terms of all the evidence available, but because the key claims are specifically comparing cigarette smoke to Camel Snus, then that's what we're asking the Committee to consider today.

But, certainly, the last question here where we're asking about discussion and the unintended users, we specifically listed youth as a population to consider during this discussion.

DR. MERMELSTEIN: Thank you.

Oh, hold on one second. Dr. Weitzman, was that clarifying?

DR. WEITZMAN: As a pediatrician, I hope that it's not an afterthought about whether or not altering labeling will influence youth. I think that that's a critical issue.

DR. MERMELSTEIN: Dr. Wackowski.

DR. WACKOWSKI: So I understand that we are being asked to consider the individual claims, that there are several claims,

but I also understand that they're being presented, proposed here as a set, together and single advertisements. So I just wanted to clarify if the order is given, can the company use any of those individual claims in isolation or must they always come together as a set, as they are presented in this application?

DR. HOLMAN: So that will be determined as we evaluate the applications. If we, in fact, determine to issue modified risk orders that would be one of the issues we would consider in issuing those orders.

DR. MERMELSTEIN: All right. Thank you, Dr. Lawrence.

Can I move on?

(Off microphone comment.)

DR. OSSIP: Thank you. So I have one question for the questions on consumer perceptions and understanding. Is that discussion restricted to the nonspecific modified risk information or does that conversation extend to the even specific modified risk, Question 1, that we're considering?

DR. KITTNER: We don't want to limit the discussion to just the nonspecific, we certainly want to hear your discussions on -- about all the modified risk information.

DR. OSSIP: Thank you.

DR. MERMELSTEIN: Thank you.

We're going to move on. Do you have your slides?

MS. HERNDON: Excuse me, this is Sally Herndon. May I ask a clarifying question, please?

DR. MERMELSTEIN: Yes. Go ahead, Sally.

MS. HERNDON: This is a question related to your slide about the phases of these applications and the opportunity for postmarket surveillance and studies. You mentioned that these applications are time limited. Can you say a little bit more about that?

DR. KITTNER: I apologize if I said the applications are time limited. The actual order is time limited, so the order is 5 years, so the --

UNIDENTIFIED SPEAKER: Maximum.

DR. KITTNER: Maximum of 5 years, thank you. So the actual order itself has a maximum of 5 years, not the application itself.

MS. HERNDON: Thank you, that's clear.

DR. MERMELSTEIN: Any other questions from people on the phone?

(No response.)

DR. MERMELSTEIN: Dr. McKinney.

DR. McKINNEY: Although the application is focused on a (g)(1) reduced risk claim, should the Committee also consider in their discussion a reduced exposure and talk about that?

DR. KITTNER: Since the Applicant is seeking a (g)(1) claim, we would like the focus of the discussion to be about that.

DR. MERMELSTEIN: Thank you.

We're now going to move on to Dr. Stepanov.

DR. STEPANOV: Good morning, everyone. I really thank you for this opportunity to share some of our data, relatively recent, that has not been necessarily written up and published in a way that could be used. I hope whatever I show today will help in discussions.

So I have this brief disclosure. Some of the data that I will be presenting was generated under grants, including tobacco regulatory science program, but it's just the content is my responsibility.

So I would like to tell you about new product watch project that have three rounds of surveys of novel smokeless tobacco products including Camel Snus, also some recent data on moist snuff that are coming from our lab and just to position to show how Camel Snus is positioned in a whole smokeless

market, and a brief comment on products, different products, that are marketed as snus.

So new product watch was a web-based national monitoring network. This initiative was partly in response to really a lack of information on novel smokeless tobacco products that would be out on the market.

There were some initial indications that they might contain lower levels of many toxicants, but data was very scarce, and we felt that it's a nice opportunity to actually monitor what happens with the products over time and provide a little bit more comprehensive information on chemical composition, including -- in addition to other characteristics.

So we had six regions in the U.S. where we collected samples of Camel Snus and also other products, not just Camel Snus.

This slide shows just some examples of how products evolved over time since they have been introduced, Camel and Marlboro here, as an example, but we also collected dissolvable tobacco and some other products that belong in this category. I'm showing this slide because we looked for -- we monitored chemical composition, but it also gives you an idea of how a product evolved over time in terms of packaging and also pouch

sizes.

Most of my presentation will include only a few chemical constituents but I wanted to acknowledge the fact that smokeless tobacco, while it does contain fewer toxicants or fewer chemicals than cigarette smoke, there is a range of toxicants and carcinogens that are present in smokeless tobacco, and it's more than just what will be presented.

Our major focus is on tobacco-specific nitrosamines that are generally accepted as a major class of carcinogens in tobacco and cigarette smoke that are specific to tobacco; they're potent carcinogens and there is enough evidence, sufficient evidence, that they do contribute to cancer development in tobacco users.

We also looked at pH and nicotine and unprotonated nicotine content. This slide just shows that very small changes in product pH can contribute to significant changes in the content of unprotonated nicotine in smokeless tobacco, and unprotonated nicotine is the biologically available form of nicotine that easily crosses several membranes and gets into the bloodstream and to the brain.

So this is the list, this slide summarizes the list of characteristics and constituents that were the primary target

of our analysis. Currently, we are completing some other analyses, like metals; we looked at PAH, and I'll be presenting data on those additional constituents.

So we received these samples, we had a very standardized protocol, standardized approach to sample collection handling between the purchase and shipment to the lab and how products were labeled, processed, deposited in the lab before the analysis. And then everything was analyzed by evidence and standardized protocols using quality control, positive control, samples to monitor for potential contribution of laboratory variations to our results.

So I will show you just some of the data and these charts, I hope you can see them, the writing, it says Camel Snus on each chart because it's part of a more comprehensive analysis of other products, as well, but for the sake of time and, I think, because of the purpose of this meeting, I'm just showing Camel Snus.

So you can see that pouch weight increased over time and that is not a secret that pouches became larger, moisture content increased, increased slightly, and pH seems to be slightly variable. Now, to explain these wide variations -- whoops, sorry. So these wide variations, that is because we

were purchasing samples from different locations. And there was a very clear pattern that products purchased from one location, all three samples would have -- you know, will be either a larger pouch size or have a higher pH or lower pH.

So on the following slides, if you see this wide variation, that is because we saw some geographical differences in the levels of these constituents or characteristics.

So this slide shows what happened to nicotine, total nicotine content slightly decreased over time between -- around one, two and three. I apologize, I didn't explain, but I hope it was clear. So these are results for round one purchases, these are results for round two and round three.

So you can see that levels of total nicotine decreased in the products. Levels of free nicotine were highly variable depending on geographical location in round one. Then there was less variation in round two and less variation in round three, so it seems like probably perfect dose of nicotine was decided on.

And last chart shows variation of free unprotonated nicotine that is dependent on pH after the three rounds. And, again, there were some changes over time, but overall you see that these variations are not as significant when you average

them. So there was some geographical variation but, overall, over time things didn't change dramatically.

Now, if you look at tobacco-specific nitrosamine content, things are quite different. In round one, this is the time when these products were known to contain very low levels of tobacco-specific nitrosamines. It was kind of an accepted fact that snus products have very low levels of tobacco-specific nitrosamines because of the way it is produced or manufactured.

Indeed, in round one we had very low levels. Then, in round two, we saw an increase and it continued going up in round three of purchases. So there was an obvious trend for NNN expressed per dry weight of product, NNK expressed per dry weight of product, and last chart shows NNN plus NNK per portion because portions also increased.

So in the third round of our purchases of these products, a single pouch was -- contained about three times higher levels of nitrosamines than pouches that were originally purchased in the first round of our survey. Now, even if levels went up and they were originally really low, so I thought it would be important to show where Camel Snus is positioned in terms of comparing with other smokeless tobacco products.

These two charts show comparison of NNN and NNK, some of

two nitrosamines between Camel Snus -- I apologize, I wish I had a pointer.

Okay. So I can go back to the slides when anybody needs clarifications, but I'm trying to use them all so I hope you can see it. So these are levels of NNN and NNK in Camel Snus and Camel dissolvable tobacco compared to moist snuff, which is most popular smokeless tobacco product. And so this is in the first round of purchases, that was in 2010, and this is in 2011. So overall, even though in the second round we have higher levels of nitrosamines in Camel Snus, they were still relatively low compared to what you see in traditional products, in traditional moist snuff. The difference is not really dramatic, so they're slightly lower.

This chart shows some more recent data in our -- one of our studies we purchased multiple samples of moist snuff, so we have about 12 different brands, each brand represented in different varieties and flavors, such as Copenhagen and Kodiak and Skoal, all the most popular moist snuff brands and they're in orange color. And at the very end, in the blue color, these are Camel Snus products from our new product watch round three.

So as you can see, there's not much of a difference in NNN levels between Camel Snus, more recent latest versions, and the

majority of smokeless tobacco, moist snuff brands that are used by those who are actually smokeless tobacco users with some exceptions. So this is a cluster of brands that overall have very variable -- levels consistently.

However, I also wanted to point out that this set, our newer set, also contained Camel Snus products that were purchased relatively recently, more recent than round three of our new product watch. And the list that we saw in this set are slightly lower than what we saw in new product watch three, so it is possible that they're going down, but it is not clear why they're so variable over time.

I am also providing this per gram dry weight data for NNN and NNK just as a reference point for what is the total content of tobacco-specific nitrosamines in these products in more recent versions that we analyzed.

Now, we also wanted to look at other key constituents, not just tobacco-specific nitrosamines, in comparing Camel Snus to moist snuff. I will consistently mark Camel Snus with blue bars and that means that everything else are samples of moist snuff products, different brands and different varieties.

So you can see that in terms of total nicotine content it's very similar to other moist snuff products. Unprotonated

or free nicotine is highly variable across moist snuff; that has been consistent throughout the years, and Camel Snus is -- has levels at the lower level, but comparable to what is -- you can see in the other moist snuff samples.

So -- I'm sorry, I'm clicking in the wrong direction. We also looked at nornicotine and nitrite and these are important constituents because they can contribute to the formation of NNN in tobacco itself, but also endogenously in users of smokeless tobacco products and again, Camel Snus has comparable levels of nornicotine to other moist snuff products on the market and comparable levels of nitrite. I actually expected that nitrite would be much lower, but it is similar to the majority of moist snuff samples that we saw.

Now, we also looked -- I'll show some data on minor -- other minor alkaloids, not just nornicotine, but anatabine and anabasine, because minor alkaloids are believed to contribute to addictiveness of nicotine, enhanced addictive effects of nicotine, and also beta-carbolines, which is a relatively recent area of interest to us because beta-carbolines can be both toxic and also contribute to addictiveness.

So anatabine and anabasine, it's all expressed per gram tobacco, is again very similar to moist snuff samples. So it

seems like Camel Snus does not really stand out in most of our analyses compared to moist snuff.

Harmane and norharmane, these are beta-carbolines. Actually, in this case harmane was similar to moist snuff products, but norharmane was lower than in most snuff products. What this means, we don't know, but interestingly enough, other snus samples also contained, which is not shown here, lower, much lower levels of norharmane than moist snuff.

Now, I did want to kind of get back to a particular importance. It seems like levels of tobacco-specific nitrosamines is pretty much what distinguishes snus from moist snuff. I just wanted to remind that NNN is a really important constituent and it has been shown to be associated with esophageal risk of development in humans.

On the other hand, it's also important to consider the levels, the other important risks. So this chart summarizes relative risk of oral cancer, larynx cancer and esophageal cancer in smokeless tobacco users compared to nonusers of any tobacco products in the U.S., in Sweden, and in India, and these are three countries that have tobacco products with very different levels of important carcinogenic constituents, including NNN.

So users of smokeless, traditional smokeless tobacco in the U.S. are at higher risk for oral cancer compared to those who use snus in Sweden, and risk is much, much higher in India where products with very high levels of tobacco-specific nitrosamines are being marketed, extremely high levels of nitrosamines in those products.

But these studies have been done recently and these were probably people who used products with higher levels of tobacco-specific nitrosamines here in the U.S. And I wanted to note that there was overall trend that we noticed in our lab towards decline in tobacco-specific nitrosamines in many smokeless tobacco products marketed in the U.S., moist snuff products. These are just some numbers that come from our laboratory. We have much more data than we publish.

So from what we saw in recent analysis, excluding Camel Snus and Marlboro snus and Skoal snus, just moist snuff samples that we had, averages approximately 1.7 µg of NNN per gram product. And data from the same laboratory conducted by the same methods, the same validated procedures, about 10 years ago levels were 2.5 µg per gram of product. And this is a consistent trend that we have been noticing.

So at this time, even if Camel Snus contains NNN levels

comparable to moist snuff, there is -- it is possible that risk due to the use of Camel Snus would not be necessarily comparable to this reported comparison.

Okay. And last point I wanted to bring up is that there are many different versions of what is called snus, so this -- unfortunately, I have separate slides to bring it up step by step, I hope it's not too busy. So this is Swedish snus -- it just doesn't work here, okay. In the upper left corner, Swedish snus with levels of NNN+ and NNK is 0.47 µg per gram tobacco product SEs and some other characteristics are listed.

U.S. snus, if you look at different brands, levels are really very different and what they tell me that probably different tobacco types are used and probably different processing methodologies are used because relative levels of NNN and NNK are different in different products in U.S. that are marketed as snus.

And then there is this, another really outrageous example of product that is marketed as snus in India that contains extremely high, some of the highest in the world, levels of nitrosamines per gram of product and also extremely high levels of unprotonated nicotine because pH of this product is 10, so it's highly alkaline, loaded with nicotine and nitrosamine

product that is also marketed as snus.

So just to summarize, the constituent profile of Camel Snus has been evolving since its first introduction to the market. Current levels of NNN in Camel Snus are comparable to what is found in many popular moist snuff brands. Interestingly, increase in NNN levels in Camel Snus occurred at the same time when we saw decreases in NNN levels in some major moist snuff brands. So it seems like agricultural or some kind of different -- or changes or trends shouldn't be responsible for the increases in NNN levels in Camel Snus.

We also see that other constituents are usually either comparable or lower in Camel Snus compared to moist snuff.

And it's also important to remember and keep in mind that products that are marketed as snus, actually not just one product, not the same product, it's a variety of different products that vary substantially in their constituent profiles and other characteristics.

And these are people who help me with my studies, and thank you.

DR. MERMELSTEIN: Thank you.

I'll take any questions from the Committee members.

Dr. Weitzman.

DR. WEITZMAN: Thank you so much. I just want to make sure the Camel Snus data that you presented is not data from the products that we're considering; is that correct?

DR. STEPANOV: And so it's not from --

DR. WEITZMAN: It's Camel Snus that precedes the --

DR. STEPANOV: No. No, it's the Camel Snus --

DR. WEITZMAN: That's currently under consideration?

DR. STEPANOV: Yes.

DR. WEITZMAN: Got you.

DR. STEPANOV: At least it looks the same. It was purchased recently. It has the same packaging as what has been earlier presented. It's the same product.

DR. WEITZMAN: Thank you.

DR. STEPANOV: Except for earlier versions where I showed how it was changing over time.

DR. MERMELSTEIN: Thank you.

MR. ZELLER: I want to follow up on that question. For the NNN data, you broke out Camel Snus in two different groups. You had round three and then more recent products.

DR. STEPANOV: Right.

MR. ZELLER: What about for the other constituents? Was

that only round three, or did that include more recent Camel Snus products?

DR. STEPANOV: Yes, I apologize. I should've made it more clear. Everything that I showed comparing to moist snuff, it's the current, recent version.

DR. MERMELSTEIN: We have a question from Dr. Herndon on the phone.

MS. HERNDON: No, I didn't have a question. Thank you.

DR. GIOVINO: This is Dr. Giovino, I have some questions.

DR. MERMELSTEIN: Go ahead.

DR. GIOVINO: Irina, thank you for your presentation. Your discussion of monoamine oxidase inhibitors, or at least that you brought it up, was quite interesting to me. But I don't know if harmane and norharmane, are they considered MAO inhibitors or are they different; do they function differently?

DR. STEPANOV: Yes, they are considered MAO inhibitors.

DR. GIOVINO: Okay. And do you know how the levels in Camel Snus would compare to the levels in Camels, combusted Camel cigarettes?

DR. STEPANOV: I do have this information, I could --

(Feedback.)

DR. STEPANOV: I could provide -- I don't remember right

off the top of my head, but I think that levels in combustible products are much higher.

DR. GIOVINO: Okay, thank you. You also discussed, obviously, changes over time in TSNA levels, which was fascinating. Do we know what the TSNA levels were at the time the epidemiologic studies were conducted? Because the people in those studies -- those studies were reported many years ago on the exposure that occurred, occurred obviously well before the studies were reported.

So do we have, obviously not from your lab, but from the scientific literature, are you aware of any indications of what the TSNA levels of moist snuff were at the time the epi studies were done?

DR. STEPANOV: Yes, that is the point that I tried to make that indeed, when these studies were conducted I believe that the levels of tobacco-specific nitrosamines in products used by study participants were much higher than what we see today in moist snuff in general and in Camel Snus in particular. And that is for -- that is for studies conducted in U.S. studies --

DR. GIOVINO: Yeah, but we don't -- unless I'm mistaken, we don't have any epidemiologic studies on the health effects

of Camel Snus published for oral cancer yet, I believe.

DR. STEPANOV: No, not that I'm aware.

DR. GIOVINO: Okay, so it really would've been moist snuff?

DR. STEPANOV: It was definitely moist snuff, yes.

DR. GIOVINO: Okay. And if I may ask one more question?

DR. MERMELSTEIN: Go ahead, Gary.

DR. GIOVINO: Thank you, Robin.

You showed a wide variability in free nicotine among many products including moist snuff products and protonated nicotine. Obviously, the brands were unlabeled, but do you have any indication that the levels of free nicotine or -- are at all related to popularity of brands?

DR. STEPANOV: Well, I think it's a well-known history of smokeless tobacco where lower -- lower unprotonated nicotine brands were marketed to beginners and then products with higher levels of unprotonated nicotine were the most popular.

We do see a lot of enthusiasm among smokers towards products like Marlboro Snus and Camel Snus that have low levels of nicotine, but I'm not sure if that is specifically the reason why people were not switching completely to these products.

DR. GIOVINO: Excellent. Thank you for your answers.

DR. MERMELSTEIN: We're going to first go to the rest of our people on the phone and then Dr. McKinney.

Dr. Thrasher.

DR. THRASHER: Yeah, thanks. So I guess my question is about the NNK data. You know, one of the public comments talks about how the NNK is a potent carcinogen that can cause lung cancer or lung tumors independent of the route of administration. Do you have any comments to respond to that, especially given that when we look at some of the data around the comparisons of NNK in snus with cigarettes, the levels are higher.

DR. STEPANOV: Right. So this is an interesting and important question. I can't cite a specific study that we are conducting now or that we published, but I do believe that it is core exposure to other chemicals that are present in cigarette smoke in the lung at the site of exposure that enhances carcinogenicity of NNN and facilitates the development of carcinogenic effects. So we don't see it as much in -- or there is no association of smokeless tobacco use with lung cancer.

However, it's unpublished evidence yet, but in places

where products contain much higher levels of tobacco-specific nitrosamines, such as in India, there is an emerging evidence of that association between smokeless tobacco use and lung cancer in users.

So it is possible that it takes a higher dose in -- when administration is oral and in the absence of other inflammatory agents and other toxicants that can enhance NNK carcinogenicity in smokers. I hope that answers your question.

DR. THRASHER: Yeah, thank you.

DR. MERMELSTEIN: Dr. Kozlowski.

DR. KOZLOWSKI: Hi, thank you for your presentation. Can you say a bit more about the magnitude or the differences in tobacco-specific nitrosamines between cigarettes and all of these moist snuff products, including Camel Snus?

DR. STEPANOV: Well, we cannot make a direct comparison because what is in cigarettes. Usually, what matters is what ends up in the smoke and is being inhaled by smokers, so you can't really make a direct comparison between per gram of tobacco and per cigarette.

Quantitatively, these are very different numbers, but I think route of exposure is important and in the end, what we see in -- based on biomarker-based studies, that smokers have

comparable exposures despite lower, quantitatively lower numbers or lower levels of nitrosamines that end up in cigarette after cigarette is burned.

So it is a complicated relationship; I wouldn't try to make a direct comparison. I think what we need to look at is biomarker-based assessment of exposure.

DR. KOZLOWSKI: Okay. And one other question. Some of the classic epidemiological studies on smokeless tobacco and cancer used dry snuff mainly. Can you make a generalization about general differences in tobacco-specific nitrosamines in dry snuff as opposed to these moist snuff products?

DR. STEPANOV: No. I don't have data on dry snuff, so I wouldn't --

DR. KOZLOWSKI: Okay, thank you.

DR. STEPANOV: -- have a comment.

DR. MERMELSTEIN: Dr. McKinney, you had a question?

DR. McKINNEY: Thank you, Ms. Chairman.

My question, it looks like when you were sampling, you started in 2010, and if I think I recall correctly, these products were regulated at that time?

DR. STEPANOV: Were they regulated?

DR. McKINNEY: Yes. Which I think they were. And so my

question is related to the change in constituents you saw at the time and the significant increase in variability. Can you comment on that and what you think is driving the variability?

DR. STEPANOV: I would not want to speculate. It could be just because levels of nitrosamines weren't necessarily the primary focus of developments that were done to product or -- I wouldn't want to speculate why.

DR. McKINNEY: Thank you.

DR. MERMELSTEIN: Dr. Bailey.

DR. BAILEY: So my question is on the same subject there about the variabilities over time. In the three rounds of sampling and testing you had, was that one round per year over 3 years or how was that sampling done again? I may have missed that.

DR. STEPANOV: So we were purchasing them over the course of several months in a particular round. I'll try to go back to --

DR. BAILEY: It's on page 6.

DR. STEPANOV: Yeah. Oh, I removed the information about it, okay. Here probably is the best way to show it, so part of round one in 2010. Over the course of several months, we reached out to our network of colleagues and they collected

samples following our standardized procedures, sent it to us to the laboratory, and once we had the samples collected as part of this particular round, we analyzed them.

And the same was done in 2011, and then third round stretched over 2 years just because we started later in the year and some products were disappearing like dissolvable tobacco was disappearing from the market and we were making efforts to chase products that we couldn't find anymore, so it took a little longer.

DR. BAILEY: So it does represent different years in the sampling and the testing. I'm just wondering if --

DR. STEPANOV: Yes.

DR. BAILEY: -- that could relate, if that variability could possibly relate to different crop years, crops of tobacco that were used to make those products. We do see some variability in NNN over time based on weather conditions when the crop was grown and that would explain --

DR. STEPANOV: That was -- yes, I think it's -- I agree, it's a good comment and I do show data for Marlboro Snus, but we saw similar trend for Marlboro Snus but not for some dissolvable tobacco products. But that is why I made a comment about trends that we saw in moist snuff nitrosamine levels.

At the same time levels of nitrosamines in snuff were declining or at least on a trend towards decline while in this particular product, at least from what I showed to you, that levels just were going up. I have been asked to maybe try to speculate the reasons, it could be the tobacco blend was changed or tobacco type that was used in making Camel Snus changed and that led to an increase.

DR. BAILEY: Right. And also, when you compare to moist snuff, I'd be interested to know if the moist snuff samples that were tested would relate to the same crop year as the Camel Snus samples that were tested. I don't know about the aging process of the snus versus moist snuff, if it would relate back to the same crop year, but we do see significant variation in NNN and other nitrosamines, just based purely on the crop year and especially curing conditions during that crop year.

DR. STEPANOV: Yes. Well, unfortunately, we can't go back in time, but -- and at that time it wasn't necessarily -- we did not know what to expect and we just wanted to monitor this particular product, not -- moist snuff wasn't part of this effort.

DR. BAILEY: Thank you.

DR. MERMELSTEIN: Dr. Wackowski.

DR. WACKOWSKI: I was wondering if you could comment on the issue and potential importance of refrigeration. I seem to recall that Swedish snus tends to be refrigerated and that's maybe another kind of important defining characteristic and if I remember correctly, when Camel Snus was first introduced, it was sold in refrigerated format and then I don't think it is anymore. So is that important and does that have anything to do with the change in levels that we might be seeing?

DR. STEPANOV: That is a good point and I would say I am a little skeptical about the need for refrigeration if it is a pasteurized product, and we did conduct experiments with storage of snus products from different places, like from India and U.S. and Sweden, compared to moist snuff and we didn't see a substantial change in nitrosamines in snus products over time over at least several months up to 6 months. It wasn't significant. So I don't think that would be an issue. And we did keep track, try to keep track, of whether or not Camel Snus was refrigerated and in first round not all of the samples were refrigerated at the place of purchase.

DR. MERMELSTEIN: Dr. Wanke.

DR. WANKE: Thank you. So I have a question about the

slide, your last slide right before the summary slide where you're comparing the Swedish, Indian and U.S. snus and I just want to make sure that I'm understanding, that I'm thinking about the numbers correctly, because you present the Swedish numbers as a combination of NNN and NNK. So to have a comparison for, say, Camel Snus would it be correct to just add those numbers in order to --

DR. STEPANOV: Right, right. So, yes. I took data for Swedish snus from Swedish Match website, as they report -- and they report NNN plus NNK.

DR. WANKE: Right.

DR. STEPANOV: That's why it is not separated.

DR. WANKE: So a simple addition would be --

DR. STEPANOV: Yes, simple addition.

DR. WANKE: So then would it be correct, then, to say that Camel Snus is about three times the amount of combined NNN and NNK as compared to Swedish? Is that, again, a correct way to think about it in the analyses?

DR. STEPANOV: Yes.

DR. WANKE: Okay. And then I also see that the Swedish snus has a nice tight range, you know, that -- is there much more variability, then, in the amount of NNN and NNK for the

American snus samples?

DR. STEPANOV: No, if you take -- if you look at one point in time and in recent products, we don't see too much of variation.

DR. WANKE: Okay, that's helpful.

DR. STEPANOV: That was something that we observed over time or geographically, but now when we look at snus products, both Camel and Marlboro, we don't see too much variability of our samples.

DR. WANKE: Okay, fantastic. Thank you.

DR. MERMELSTEIN: Dr. Tomar on the phone.

DR. TOMAR: Oh, thank you. Irina, thank you for the presentation. I've got a couple of things I just wanted to try to clarify, actually, not so much to your talk but some of the -- some of the questions that were posed by other Committee members.

So there was a comment made a couple of -- a couple presenters back made the statement that these products were regulated by FDA in 2010. I wasn't sure exactly what aspects of regulation that that questioner was referring to. To my knowledge, there still are no -- currently no product standards and presenting levels of TSNA or other toxicants in these

products; is that correct?

DR. McKINNEY: Sir, let me -- the reason I asked the question is because any changes to the product you have to receive authorization and so my question was about the changes in the constituents that you see when the industry, to be compliant with the laws, not making changes to the product.

DR. TOMAR: Okay, I thank you.

And if I could just ask, you know -- and Irina, maybe this question is for you. So we talked about NNN being a -- I mean NNK being a carcinogen for -- implicated in lung cancer.

In the one cohort study that I'm aware of, they looked at change in lung cancer risk among people who had completely switched from cigarettes to using smokeless tobacco, there was a significantly elevated risk for lung cancer mortality compared with those who completely quit all tobacco use. Could that elevation possibly be due to accumulative exposure to NNK among former smokers who switched to a smokeless tobacco product?

DR. STEPANOV: In theory, it could be because they're still exposed to a lung carcinogen and potentially other -- not just NNK, also inflammatory agents. We know that inflammation also contributes to lung cancer, it's an underlying key

mechanism.

Metals, tobacco is one of the probably major sources even though cadmium is not extremely high in tobacco compared to other dietary sources, but it is a source of exposure to cadmium that is also lung carcinogen.

So in theory it could be, but again, if study was not designed to specifically ask this question, it's hard to be really confident in making such conclusion.

DR. TOMAR: All right, thank you.

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: Could you clarify again on the slide that we're seeing here, next to the last slide, the group of Camel Snus products that you measured for this comparison or that were measured for this comparison, is it the current group that we're considering? Is it the aggregate of all six or is it particular ones?

DR. STEPANOV: This is average of all six and each of these varieties have multiple samples. Three, I think at least three samples that we purchased from three different retail shops. So this is an average for the recently purchased Camel Snus.

DR. OSSIP: Anything you can comment on the variability

that may have been observed across the individual products?

DR. STEPANOV: There was some variability, but I would say it's not dramatic, it's -- it could be it is larger than what's here, is reported for Swedish snus, but not significant.

DR. OSSIP: Thank you.

DR. STEPANOV: I would be happy to provide this actual data, raw data, if that is of interest. Unfortunately, I did not summarize it here in the way that would be helpful and I don't want to trust my memory with specific standard deviations for these measurements.

DR. OSSIP: Thank you very much.

DR. MERMELSTEIN: Dr. Bierut.

DR. BIERUT: Thank you for the presentation. I need help with the comparison between snus and combustible cigarettes and I understood you to say that we really -- it's difficult to measure as part of the product because of the way the product is administered. But if we measure it as a biomarker, so if a person ingests one -- or uses one pouch or uses one combustible cigarette, what would the relationship be between the biomarker of exposure to NNN and NNK?

DR. STEPANOV: Again, this kind of direct pouch to cigarette comparison has not been done, but studies that had

people switching, let's say, from smoking to using smokeless product, to using snus, show that -- I know there are studies that I have been part of. Smokers completely switching to Swedish snus had significant reduction in their biomarker of NNL, which is biomarker of exposure to NNK. NNN at that time was not measured.

But there is also more recent study where people switched to Camel Snus and reductions in NNL were not as dramatic in those who completely switched after 4 weeks, I think, of Camel use and there were no reductions in NNN, no differences between baseline and when they used Camel Snus, which makes sense.

DR. BIERUT: So let me just clarify. So you're saying that when you looked at the difference between people who were using combustible and then switched to some Camel Snus there was no change in the biomarkers?

DR. STEPANOV: In this particular study there was no statistically significant difference between urinary NNN biomarker at baseline and at 4 weeks of using Camel Snus.

DR. BIERUT: Thank you.

DR. MERMELSTEIN: Dr. Johnson.

DR. JOHNSON: Yes, thank you for a very interesting presentation. I have one question about the slide that's up

right now. With regard to the Swedish snus data that you are showing, okay, this came from their website, I see, and was this as in the product as sold and used or was this dry weight? So that we can make comparison.

DR. STEPANOV: All the numbers here are per gram of product as used.

DR. JOHNSON: Okay. And the data that's used over here for U.S. snus, is that as used or dry weight?

DR. STEPANOV: Everything on this slide is per gram of product as used, including Indian, U.S., and Swedish products.

DR. MERMELSTEIN: Okay, thank you. Thank you very much, Irina. Great presentation, very, very good.

We're going to now take a break. We're a little behind, so let's do a 10-minute break and start back here at 10:10. Thank you.

(Off the record at 9:58 a.m.)

(On the record at 10:10 a.m.)

DR. MERMELSTEIN: Before we move to the presentation by R.J. Reynolds, we still have one follow-up question from a Committee member on the phone to Dr. Stepanov, if you want to just go to the mike over there, and from the phone, Dr. Herndon.

MS. HERNDON: Sally Herndon.

I had a follow-up question to an earlier question about any studies you may or may not be aware of about the levels of NNN and NNK in people who are dual users. The studies you discussed were people who completely switched from e-cigarettes to snus products, and I wonder about dual users and the level of NNN and NNK as the biomarkers.

DR. STEPANOV: Yes. So dual users have the same levels of NNL and NNN in their urine as smokers. There's no reduction in exposure in dual users. And I think this is pretty consistent in our studies and other reports.

DR. MERMELSTEIN: Thank you.

DR. KING: Just to clarify, is there an increase or there's just no change, no difference?

DR. STEPANOV: I think it's inconsistent, it depends on what dual use means, so how much of a dual use is taking place. If it is on the top of regular smoking, you would expect there to be an increase. If it is substitution, partial substitution, which is what happens in our studies where we ask people to switch or offer them the product and they end up using both smoking and using smokeless, they have no change in NNAL and NNN in their urine.

DR. MERMELSTEIN: One last from Dr. Bierut.

DR. BIERUT: I had the same question.

DR. MERMELSTEIN: All right. Thank you very much. We're going to move now to the presentations by R.J. Reynolds.

DR. OGDEN: Good morning. My name is Mike Ogden, and I'm Senior Vice President of Scientific and Regulatory Affairs for RAI Services Company. My department coordinates FDA compliance activities on behalf of all of Reynolds American's operating companies.

My colleagues and I are very pleased to have this chance to meet with you this morning to discuss the modified risk tobacco product applications for Camel Snus that we have submitted on behalf of R.J. Reynolds Tobacco Company.

During our presentations we're going to provide what we believe is clear, consistent, and compelling evidence that marketing Camel Snus as a modified risk tobacco product will not only benefit individual adult smokers but will also have a net positive impact on U.S. public health.

In particular, we plan to demonstrate that smokers who switch completely to Camel Snus can greatly reduce their risk for lung cancer, oral cancer, respiratory disease and heart disease, and that authorizing the proposed modified risk

advertising for Camel Snus will likely yield a net health benefit for the population as a whole.

As you will hear this morning, consumer research and statistical modeling confirm that the benefits of advertising Camel Snus as a lower-risk alternative for adult smokers will greatly outweigh unintended consequences. And the proposed modified risk advertising should prompt a sufficient level of switching to produce an overall reduction in population risk.

Before we begin, I'd like to emphasize what we believe is an important consideration in our efforts to migrate smokers away from cigarettes and it's this: There is no one-size-fits-all product or program that will dramatically reduce the death and disease caused by cigarettes. Different types of reduced risk tobacco and nicotine products appeal to different individuals. And no matter how good the product or its advertising and promotion are, neither Camel Snus nor any other lower-risk tobacco product can, on its own, accomplish that public health goal.

But we firmly believe that clearing Camel Snus as a modified risk tobacco product is a strong, scientifically sound first step in effectively educating the public about the benefits of switching to lower-risk tobacco products like Camel

Snus.

So here's what we're going to present to you this morning. I'll start off with a brief history of Camel Snus and an overview of the product's development and design. Then I'll walk you through important details about the three proposed modified risk advertising executions that we've submitted to the Agency.

After that, my colleagues will present scientific evidence showing that individual health risk will be reduced when smokers switch to Camel Snus; that the proposed MRTP advertising is well understood and communicates accurate information about the risk of using Camel Snus relative to smoking; that the proposed advertising attracts interest primarily from smokers who can benefit from switching to snus; and that the population, as a whole, will benefit from the resulting reductions in risk.

Here, specifically, is what each of our presenters is going to cover.

After my overview of the product and the proposed advertising, Dr. Kristin Marano will lead us through the epidemiology relevant to Camel Snus.

Dr. Elaine Round will present both the clinical and the

preclinical results that outline the mechanism for the reduced risk seen in the epidemiology.

Dr. Saul Shiffman of Pinney Associates will review the results from our risk perceptions, comprehension, and likelihood of use testing of the modified risk advertising that is before you today.

And, finally, Dr. Geoff Curtin will walk you through the results of rigorous population modeling which demonstrates the MRTP's great potential for a positive impact on public health.

After that, I'll be back to wrap up the presentation and then Dr. Shiffman will serve as moderator during our post-presentation discussion.

As you know, the tobacco and nicotine product risk continuum lies at the heart of tobacco harm reduction. As illustrated here, it is very well established that cigarettes present the highest risk with nicotine replacement therapies presenting the lowest risk.

A large body of scientific evidence confirms that smokeless tobacco products like Camel Snus lie very near the lower end of the risk continuum and that's due to the fact that smokeless tobacco doesn't expose users to the toxicants produced by the combustion of tobacco.

That being the case, many respected researchers and public health professionals, including Abrams, Kozlowski, Sweanor, to name a few, agree that consumers of tobacco products need to be accurately informed about the relative risks of these products to encourage those who do not want to quit completely to migrate to products that present lower risk, and that is exactly what the proposed modified risk advertising for Camel Snus is designed to do.

Camel Snus has been on the market for more than a decade, and as you heard this morning, its availability is not the subject of the applications we filed with FDA. Rather, our applications seek authorization to provide consumers with accurate information about relative risk balanced with appropriate cautionary information. I'll show you the proposed advertising shortly, but before I do I'd like to provide an overview of the product and how it's made.

Camel Snus is a spitless, pouched, smokeless tobacco product that was introduced by R.J. Reynolds in 2006. The fact that it comes in a pouch and spitting isn't required makes it more convenient and more acceptable to many smokers than other smokeless tobaccos. And, importantly, it was specifically designed to have the same risk reduction characteristics as

Swedish snus.

And I'll start with a bit of history. As you know, over the past several decades, Swedish smokers migrating from cigarettes to snus have experienced a dramatically reduced incidence of tobacco-related disease and mortality, giving Sweden the lowest rates of any country in Europe. R.J. Reynolds wanted to help replicate those results here in the United States by offering American smokers the opportunity to lower their risks by switching from cigarettes to snus.

So a team of Reynolds researchers went to Sweden in 2005 and worked with a Swedish snus manufacturer to develop a product for the U.S. market that had the same risk reduction characteristics as Swedish snus. To that end, Camel Snus uses the same low toxicant tobacco types and it has the same basic formulation as Swedish snus.

To make the product appealing here in the U.S., the flavors were adapted to the American palate using ingredients commonly used in existing smokeless tobacco products and ingredients commonly used in foods.

Camel Snus is manufactured using the same production methods as Swedish snus, so unlike most smokeless tobacco products in the U.S., it's heat treated rather than fermented.

Low toxicant, finely milled tobaccos are mixed with water and salt and then heat treated to stabilize the mixture and produce a product that maintains the low tobacco-specific nitrosamine levels that naturally occur in the low toxicant tobaccos used in Camel Snus.

A buffering solution is then added to stabilize the pH and the product undergoes additional heat treatment. Humectants and flavorings are added to condition and flavor the tobacco and finally, the product is portioned and packed in fleece pouches.

The six variants of Camel Snus that are currently on the market in the United States are shown here. As you can see, they come in two sizes. Three styles come in a 600 mg pouch and the other three are in a 1,000 mg or 1 gram pouch. One flavor, Camel Snus Frost, is available in both 600 mg and 1 gram sizes.

The MRTP applications that we submitted to the Agency are seeking FDA orders to permit modified risk messaging through a variety of advertising media under Section 911 of the Tobacco Control Act. I want to be very clear about this point, the orders would authorize very specific modified risk messaging providing adult smokers with accurate, easily understood

comparative risk information and it is the ads in their entirety, as I will show them to you, that R.J. Reynolds would use.

I want to note that we're also not proposing any changes to the label of the product or to the mandated government warnings.

I'll also point out that the authorization to advertise Camel Snus with modified risk messaging would be subject to postmarket surveillance.

So now that we've gone through what Camel Snus is, how it's made, what the finished product looks like, let's take a closer look at the modified risk messaging for which we are seeking authorization.

As you know, there are three versions or executions of the advertising. They were developed through an iterative process that was shaped by learnings from qualitative panels and other relevant sources. This process helped us understand the importance of presenting clear, accurate scientific information using language and graphics that are easily understood by and appeal to adult smokers.

As you've seen in our applications and our briefing book, the three versions are very similar but there are some

important differences that I'll highlight as I go along. In the interest of time, I'll focus this morning on the version that we refer to as Advertising Execution Number 2, which you see here.

Each of the three print ad executions has three panels that each feature one of the mandated government warnings. I'll spend a few minutes talking in more detail about the content of each of these panels. The first panel features a short, simple message along with a picture of the product. The second panel tells smokers what Camel Snus is, how it's different, and how it's used. And the third panel talks about the difference in risk between cigarettes and Camel Snus. This panel also contains substantial balancing information to make sure that smokers don't get the impression that Camel Snus or any other tobacco product is safe.

Here's the first panel of Execution 2. It introduces the opportunity for adult smokers to reduce risk with the headline "No Smoke, Less Risk, Choose Snus."

The message to switch from cigarettes to Camel Snus is visually conveyed by the crushed cigarette at the bottom of the tin. And as with each of the three panels in all three advertising executions, it features the mandated government

warning.

Here's the second panel. As you can see, the left-hand column describes the product and its use with a section titled "What is Camel Snus? How is it different? How do I use it?" I want to point out that last bullet in the "What is Camel Snus?" section. It emphasizes that Camel Snus contains nicotine and is addictive. The right-hand column is an infographic that emphasizes -- sorry, that describes the product's ingredients, sizes, flavors, quantity, and typical use duration.

And here's the third panel. As you can see, it contains three main message sections. The top left section contains the key modified risk statement. This statement differs some in all of the executions, and I'll detail those differences shortly. The bottom left section answers the question "I'm a smoker. Why should I switch?" In the section at the middle right, which is titled "No tobacco product is safe," contains substantial balancing information, again to make sure that smokers don't get the impression that Camel Snus or any other tobacco product is safe.

Now I'll go into more detail about each of the sections in the next few slides and starting with the section on the top

left. This is the "No Smoke = Less Risk" section of Advertising Execution 2. The text in this section contains the key modified risk statement. It's essentially the same in all three executions, but there are some slight variations.

But before I point out the differences in that top box, let me first walk you through the text in the middle and bottom boxes of Execution 2. The middle box says scientific studies have shown that Camel Snus contains less of the harmful chemicals than cigarette smoke, for example, tar, carbon monoxide. The bottom box says Camel Snus is smoke free, so there are no secondhand smoke risks for you or those around you.

Now, let's compare the text in the top box of each of the three advertising executions. So here are the key modified risk statements in the three executions.

Execution 1 on the top left says, "Smokers who switch completely from cigarettes to Camel Snus can significantly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease."

Execution 2 in the middle puts more emphasis on "switch completely" by underlining it and writing it in all capital letters. And it also changes the word "significantly" to

"greatly."

And at the bottom right is the key modified risk statement in Execution 3. The only difference between statements in Executions 2 and 3 is that Execution 3 mentions only two of the four diseases: lung cancer and respiratory disease.

The "benefits of switching" box highlighted here notes that snus has less of the harmful chemicals that are found in cigarette smoke. It poses the best risk for both the smoker and also for those around the smoker. There's no lingering smoke smell, and it's hassle-free tobacco.

The balancing information box shown here contains prominent balancing information to ensure that smokers understand that no tobacco product is safe, that Camel Snus contains nicotine, which is addictive; adults who don't use or quit using tobacco products shouldn't start; minors and pregnant women should never use any tobacco product; quitting is the best choice for smokers who are concerned about the health risks of smoking; and smokers who don't expect to quit should think about switching to Camel Snus.

So here once again are all three panels of Advertising Execution 2. As you've seen, the information is presented in a clear, easy-to-understand manner that breaks the information up

into bullet points that are grouped or chunked by topic. The messaging also uses bold, standout headings, including some questions, to attract attention and clearly indicate the particular topic for each section.

I would also like to note that the characteristics of how these ads are written, how they're illustrated, how the information is arranged, is all consistent with CDC's best practices for health communications.

So that's an overview of Camel Snus and our applications to get clearance from the FDA to advertise it using again the very specific modified risk messaging submitted with these applications.

The remainder of our presentations this morning will highlight the extensive body of scientific research that supports the accuracy and the applicability of that modified risk messaging and the positive impact it can make on U.S. public health.

So now I'll turn it over to my colleague, Dr. Marano, who will discuss the epidemiology of smokeless tobacco in general and of snus in particular.

Dr. Marano.

DR. MARANO: Good morning, I'm Kristin Marano, an

epidemiologist and Director of Scientific and Regulatory Affairs at RAI Services Company. I'm pleased to be here today to talk with you about the epidemiological evidence that supports our proposed modified risk advertising for Camel Snus.

We are proposing to communicate to current adult smokers that switching completely to Camel Snus can significantly reduce their risk for lung cancer, oral cancer, respiratory disease, and heart disease. While no tobacco product is safe, the epidemiology demonstrates that smokeless tobacco use significantly reduces the risk for these diseases compared with cigarette smoking, and switching completely to smokeless tobacco will result in significantly reduced risks.

In addition, smokeless tobacco use reduces the risk for most other tobacco-related diseases, including all-cause mortality, compared with cigarette smoking.

Epidemiology allows us to evaluate the real-world impact of tobacco products as actually used on actual morbidity and mortality. There's a large body of epidemiological evidence from both the United States and Sweden that consistently shows significantly reduced risk for smokeless tobacco users compared with cigarette smokers for these four diseases.

And there's scientific consensus that smokeless tobacco

use presents significantly reduced risk compared with cigarette smoking for these four diseases. This isn't surprising because cigarette smoking involves combustion and the inhalation of combustion products and smokeless tobacco use does not. What I'm going to show you today are representative results from the epidemiological studies. After that, I'll provide you the rationale for why these results are relevant to Camel Snus.

In our modified risk application for Camel Snus, we reviewed and summarized the large body of epidemiological literature including primary literature, meta-analyses, and review articles for smokeless tobacco users relative to cigarette smokers for these four health outcomes.

Also included in our application is an externally conducted systematic review of the literature pertaining to the risks of these four diseases among smokeless tobacco users. There are many studies that have examined these relationships and the results are clear and consistent.

In the interest of time, I'm going to focus on two key examples, a large cohort in the United States and a large cohort in Sweden. Studies that utilize these cohorts are considered landmarks in the field and their results are representative of the large body of literature demonstrating

significantly lower risk for smokeless tobacco users compared with cigarette smokers.

This slide shows data from the Cancer Prevention Study II carried out by the American Cancer Society in the United States. The figure shows mortality risks for cigarette smokers, the red bars; switchers from cigarette smoking to smokeless tobacco use, the blue bars; and smokeless tobacco users, the gold bars, for the four diseases in the proposed risk claims.

These data clearly demonstrate that smokeless tobacco use presents lower mortality risks than cigarette smoking for lung cancer, oral cancer, respiratory disease, and heart disease.

A few things about this figure, the vertical line at one represents never users of tobacco as a point of comparison. Solid bars represent statistically significant differences for never users of tobacco and open bars represent non-statistically significant differences for never users of tobacco. There's no blue bar for oral cancer because no value was reported in the study; we'll talk about that more later.

For now, let me review the findings for each disease starting with lung cancer. You can see the magnitude of the difference is striking. The risk of dying from lung cancer is

over 20 times higher in smokers compared with never users. We know that, historically, lung cancer was seen almost exclusively in cigarette smokers. The risk for switchers is one-fourth of that of smokers and the risk for smokeless tobacco users is one-tenth of that of smokers. Overall, we see very large differences between smokers and smokeless tobacco users and a clear benefit to switching.

Turning to oral cancer, although perhaps counterintuitive, given it's a tobacco product placed in the mouth, the oral cancer risk for smokeless tobacco users is much less than the risk for cigarette smokers.

In these CPS-II data, oral cancer mortality is more than 10 times higher in cigarette smokers than in never users of tobacco, and note that the oral cancer mortality risk for smokeless tobacco users is not different than one.

Based on their own review of the epidemiological literature, the Surgeon General's 2014 report on the health consequences of smoking stated that "Epidemiological studies of smokeless tobacco indicate that it increases the risk of oral cavity...[cancer], at least for some forms of smokeless tobacco. The associated risks...are less than the risk...from smoking."

CPS-II didn't have data on oral cancer risk among switchers. But given the data, including the difference in oral cancer risk between smokeless tobacco users and smokers, as well as the reductions observed for the other diseases, we would expect significant reductions for switchers as well.

Although we don't have data on oral cancer for switchers from CPS-II or the Swedish construction workers cohort, we do have switching data from Sweden. It's a case-control study with 354 incident cases of oral cancer.

This slide shows smokers in red from cigarette smoking -- I'm sorry, switchers from cigarette smoking to snus in blue and snus users in gold. These data demonstrate significantly lower risks of oral cancer for cigarette smokers who switched to snus.

This slide shows data for chronic obstructive pulmonary disease. Like lung cancer, COPD is strongly associated with cigarette smoking and smokers are more than 10 times as likely to die of chronic obstructive pulmonary disease than never users of tobacco, and the risk for smokeless tobacco users is much lower. Note the open bar for smokeless tobacco users, which indicates the risk is not statistically significantly increased relative to never users of tobacco. Those who

switched to smokeless tobacco still carry some risk which is likely due to residual risk from former smoking, but the risk is a third of that of cigarette smokers.

Finally, heart disease. The story is as consistent for coronary heart disease as it is for the other diseases. The risk for cigarette smokers is about three times that of never users. Although you can see that the magnitude of risk is less than that of the other three diseases, this is because heart disease is very common and there are many causes of heart disease other than smoking. As a result, the rate of heart disease may be increased even without tobacco use.

However, you can see here the more than 50% reduction in risk for both smokeless tobacco users and switchers relative to cigarette smokers.

These data clearly demonstrate that the risk of using smokeless tobacco is significantly less than that of cigarette smoking for these four diseases. Switchers also have significantly reduced risk.

The results presented thus far have been representative of tobacco users in the United States, but you may be more familiar with the story of snus use in Sweden, what's commonly referred to as the Swedish experience.

These data are from Sweden and reflect the incidence of disease in the Swedish construction workers cohort. More than 250,000 men were part of this cohort.

Consistent with the findings from the United States, we see a clear demonstration of lower risk among snus users, the gold bars, and higher risk among cigarette smokers, the red bars, for both lung cancer and oral cancer.

Comparable data are also available from the Swedish construction workers cohort for respiratory symptoms and heart disease, and these data continue to confirm significantly lower risk for snus users relative to cigarette smokers.

In total, data from both the United States and Sweden demonstrate that smokeless tobacco use, including snus, presents significantly less risk than cigarette smoking. Notably, evidence from these specific studies are consistent with the larger body of epidemiological evidence demonstrating reduced risk for smokeless tobacco users relative to cigarette smokers.

Not surprisingly, these data are not specific to Camel Snus. All epidemiological studies, by their nature, evaluate categories of products like combustible cigarettes and non-combustible smokeless tobacco products. They don't evaluate

any single brand or style, but rather include multiple brands and styles.

These data, however, are relevant to Camel Snus, and here's why. Keep in mind it takes many years for tobacco-related morbidity and mortality to become evident. As a result, the epidemiological outcomes that you've seen today reflect the effects of smokeless tobacco products that study participants began using many years ago.

So the question to consider, then, is this: What were the nature and characteristics of the smokeless tobacco products whose effects are reflected in the epidemiology I've shown you?

Those products were smokeless tobacco products with the types of toxicants like those in Camel Snus; however, those products had a higher level of -- higher levels of toxicants than Camel Snus and those products were consumed more frequently and in greater amounts than Camel Snus. Let me show you what I mean by first talking about toxicants using tobacco-specific nitrosamines, or TSNAs, as just one example.

TSNAs are well-studied constituents in tobacco that are identified on FDA's established list of harmful and potentially harmful constituents. This slide shows TSNA data, specifically NNN and NNK, for two leading U.S. smokeless tobacco products,

Brand A and Brand B, between 1980 and 1992, in blue. Camel Snus is represented in gold on the right.

These data demonstrate that levels of tobacco-specific nitrosamines are significantly lower in Camel Snus than in historical U.S. smokeless tobacco products. It's possible that the levels before 1980 were even higher.

These data demonstrate that Camel Snus has significantly lower TSNAs than the U.S. smokeless tobacco products reflected in the U.S. epidemiology studies.

The same pattern holds true for the Swedish data, seen here. Levels of tobacco-specific nitrosamines, NNN and NNK, in Camel Snus, the two gold bars on the right, are significantly lower than the NNN and NNK levels in Swedish snus between 1980 and 1992, the blue bars. In total, both in Sweden and the United States, the epidemiology which shows reduced risk for smokeless tobacco use is relevant to Camel Snus, which has lower TSNAs than the products reflected in the epidemiology.

So we've talked about toxicants using TSNAs as just one example; however, when we think about exposure, usage patterns, how much you use and how often you use, are also important. And usage of Camel Snus is lower than historical smokeless tobacco products.

This slide shows usage of Camel Snus, in the left column, is less than the usage of historical U.S. smokeless tobacco products, in the right column. For example, the average amount of Camel Snus used per day is approximately 3 to 5 g, whereas the average amount of historical U.S. smokeless tobacco used per day ranges between 7 and 20 g.

Taken together, what this all means is that given lower toxicant levels in Camel Snus and given lesser usage of Camel Snus, there is less exposure to toxicants. So it's clear that the U.S. and Swedish epidemiological studies are relevant for estimating the disease risks of Camel Snus and in fact, are likely to overestimate the risks.

In summary, the epidemiological evidence from both the United States and Sweden demonstrates that smokeless tobacco use presents significantly less risk than cigarette smoking.

The epidemiological evidence supports the purposed modified risk statement that smokers who switch completely to Camel Snus can greatly reduce their risk for lung cancer, oral cancer, respiratory disease, and heart disease.

This epidemiological evidence is also consistent with the clinical and preclinical data that Dr. Round will now present.

DR. ROUND: Good morning. My name is Elaine Round, I'm a

Senior Director in Scientific and Regulatory Affairs at RAI Services Company, and this morning I'll present a summary of the clinical and preclinical research included in the application.

We conducted a variety of human studies that examined the use of Camel Snus and the resulting exposure to harmful and potentially harmful constituents compared to smoking. We also conducted preclinical studies using assays that are standardly used to assess the toxicity of products and that had relevance to the four disease endpoints included in the modified risk advertising. And as you'll see, the entire body of clinical and preclinical evidence is consistent with the epidemiology and supports a reduction in health risk compared to smoking. First, let me show some data from our human studies.

In total, Reynolds conducted eight clinical studies with varying designs and endpoints, and the results of five additional human studies have also been published by other groups. The endpoints in these studies included assessment of product use amounts, nicotine pharmacokinetics, mouth-level exposure, and biomarkers.

Mouth-level exposure tells us about the amounts of constituents removed from the pouch during use and there's

compelling data that show a large faction of constituents in the pouch remain there after use. This is helpful to understand the exposure to constituents for which suitable biomarkers don't exist. Where they do exist, biomarker levels are the most important endpoints to consider when assessing exposure to tobacco constituents.

Biomarkers measure the exposure to harmful and potentially harmful constituents regardless of the amounts present in the tobacco product of interest, either in the snus pouch itself or in cigarette smoke. Biomarker levels take into account both the chemistry of the product which equates the constituent levels in the product and the way the products are used, including the amount used per day, the amount of time the product is used, and the route of exposure. So the biomarker levels reflect actual exposure.

The constituent levels in a product and what actually gets into a user are very different. So let me show you an example with nicotine.

What you see here are the minimum and maximum nicotine values measured in the Camel Snus pouch relative to the levels found in mainstream cigarette smoke shown as a percent. The mainstream smoke values are represented as the red line at 0%,

against which the Camel Snus values are compared. As you can see, the amount of nicotine in a Camel Snus pouch is about 250 to about 750% higher than the levels found in mainstream cigarette smoke.

In comparison, on the right, you see biomarker levels for nicotine exposure in exclusive Camel Snus users from two studies compared to the biomarker levels found in exclusive smokers. Here, the biomarker levels of the smokers are represented by the red line at 0% with the blue bars representing the differences observed in the Camel Snus users. Despite the much higher levels of nicotine found in the Camel Snus pouch compared to cigarette smoke, Camel Snus users are exposed to slightly less nicotine than cigarette smokers. So as you see, the constituent levels in a product and what actually gets into someone who's using the product are very different.

For that reason, I'll focus the rest of my discussion of the human studies on the biomarker results. First, I'll show you biomarker data from a study we conducted to measure the exposure levels in people who naturally adopted different types of tobacco products and who use the products as they choose.

Here, I'll focus initially in data from exclusive smokers,

exclusive users of Camel Snus and people who didn't use tobacco at all. Again, these are people who, in the real world, use these different products and use them however they choose or don't use any tobacco products at all.

The corresponding biomarker levels reflect how people are using the products or not in the real world. Also, keep in mind that the smokers' exposure is the baseline against which we'll compare the other groups. I'll show you the biomarker results grouped by relevance to disease endpoint.

So, first, let's look at the biomarkers of constituents related to cancer. Shown here in gray are biomarker results from the non-tobacco use group presented relative to cigarette smokers. The red line at 0% indicates the average level of each biomarker seen in the cigarette smoker group. So this is the reference point for the differences we see compared to smokers.

Differences from the smoker group are expressed as a percent with the reductions indicated as a negative percent extending below the red line. Solid bars indicate statistically significant changes and open bars will indicate no statistical significance.

The compounds here are all designated as carcinogens on

FDA's established list of harmful and potentially harmful constituents in tobacco products and smoke. And all are generated during the combustion of tobacco that occurs during smoking.

The non-tobacco users' exposure to these constituents is substantially lower and significantly significant compared to smokers. You'll notice that the reductions aren't a hundred percent for non-tobacco users because there's still exposure to these constituents through the environment and through food.

Now let's look at the blue bars which represent the exposure to the Camel Snus group. Again, you see generally significant differences that are substantially lower than the smoker group and perhaps more importantly, for most constituents the Camel Snus results look very similar to the non-tobacco use results. These results are consistent with Camel Snus, not combusting tobacco during use.

Now, on the right, you see the results for two carcinogens that are present in unburned tobacco, NNN and NNK. Because they're present in tobacco, we would expect Camel Snus users to be exposed to them during use. Here, the differences are not statistically significant compared to smokers, that is they're not reliably lower or higher, so exposure is neither increased

nor decreased.

And, finally, you see the results for urine mutagenicity, which can be considered a composite measure of the mutagenicity of the products of combustion. Here again, the difference is substantially and significantly lower for the Camel Snus group and similar to the non-tobacco use group.

Results of exposure to all of the carcinogens in totality suggests that overall, users of Camel Snus are exposed to lower levels of carcinogens than cigarette smokers. This is consistent with the epidemiology for lung cancer and oral cancer and helps explain why the risk of lung and oral cancers is so much lower for users of smokeless tobacco products like Camel Snus compared to smokers.

Now let's look at the biomarker results for constituents designated as respiratory toxicants on FDA's list of HPHCs. All of these are generated during the combustion of tobacco and similar to the results for the combustion-related carcinogens on the previous slide, we see generally large significant reductions with the Camel Snus group compared to smokers and the results are similar to those of the non-tobacco use group.

In addition, the route of exposure to these constituents is quite different for Camel Snus users than it is for smokers.

Unlike smoking, direct exposure to respiratory tissues doesn't occur with Camel Snus use. These results are consistent with the epidemiology for respiratory diseases such as COPD and help explain why the risk of respiratory disease is lower among users of smokeless tobacco products, like Camel Snus, relative to smokers.

And, finally, let's look at the biomarker results for constituents designated as cardiovascular toxicants on FDA's list of HPHCs. Carbon monoxide is also added here due to its strong scientific support as a biomarker for cardiovascular risk.

All of these are generated during the combustion of tobacco and similar to the results for the combustion-related toxicants on the previous slides, we see large significant reductions in the Camel Snus group compared to smokers. And the results are similar to those of the non-tobacco use group. These results are consistent with the epidemiology for coronary heart disease and explain why the risk of heart disease is lower among smokeless tobacco users of products like Camel Snus relative to smokers.

Now let's look at some data from the same study that also includes natural adopters of dual use of cigarettes and Camel

Snus. Dual use of Camel Snus and cigarettes can be a transition state to complete switching. Keep in mind, dual use is not the intended use of the product, as the proposed advertising emphasizes that smokers should switch completely to Camel Snus. And the results you'll see here are in the absence of the modified risk advertising, so the data reflect use without the risk communication. The data will be presented in the same way as the previous three slides, but has the biomarker results from the dual use group in purple.

What you'll see here is similar across the three toxicant categories. Dual use of Camel Snus and cigarette smoking does not statistically significantly increase the exposure to tobacco toxicants compared to smoking alone. Here we're specifically looking at carcinogens. And notice that the composite measure of the combustion related mutagens in the urine of participants is significantly lower than exclusive smokers.

In the interest of time, I won't show you the results for the respiratory and cardiovascular toxicants, but we see similar results for all of those as we do for the carcinogens here. So even with dual use among natural adopters who would use the products and use them as they choose, exposure to

carcinogens, respiratory toxicants, and cardiovascular toxicants is not increased.

While these are the results of one study, we consistently see some significant reductions in constituent exposures and no significant increases in exposure in other studies that also included dual use. And looking at all the constituents together, the conclusion can be made that while the proposed advertising emphasizes switching completely to reduce health risks, this data shows that dual use with cigarettes, as people choose to use the products, will not increase health risks relative to exclusive smoking.

Now let's look at data from a study in which smokers were switched completely to Camel Snus. These data will show the potential for what can happen if smokers adhere to the modified risk advertising. Participants in this study resided in the clinic for their entire participation, which was 1 week, and they smoked for the first 2 days, so they served as their own baseline. I'll show you data from 5 days of either exclusive Camel Snus use or abstinence compared to the smoking baseline.

Similar to the last study, the next three slides show all of the biomarkers were measured for constituents on FDA's established list of HPHCs according to disease endpoint.

However, a few more were included in this study than the last. They're formatted in the same way, but here participants served as their own baseline. So these are the differences from their baseline smoking control, which is represented by the red line at 0%.

For the carcinogens measured in this study, we see consistently large statistically significant decreases in exposure to those generated during combustion when smokers switched to Camel Snus and the decreases are almost exactly the same as switching to abstinence. This also includes the composite measure of mutagens in participants' urine. And there are no increases in the carcinogens present in unburned tobacco. These results, taken in totality, show an overall reduction in exposure to carcinogens when smokers switched completely to Camel Snus use.

And now on to the respiratory toxicants. Here we see generally large significant reductions with the Camel Snus group compared to smokers and again, these reductions are very similar to the abstinent group. Overall, exposure to respiratory toxicants decreased when smokers switched completely to Camel Snus use similar to abstinence.

And then, finally, the cardiovascular toxicants. Here

again, we see generally large significant reductions with the Camel Snus group compared to smokers and those reductions are very similar to those of the abstinence group. So exposure to cardiovascular toxicants decreased when smokers switched completely to Camel Snus similar to abstinence.

And, overall, the results from this switching study support the epidemiology behind the proposed modified risk advertising statement that smokers who switch completely to Camel Snus can greatly reduce their risk of disease.

And, taken together, the biomarker results from both studies clearly demonstrate that exclusive use of Camel Snus exposes individuals to significantly lower levels of carcinogens, respiratory toxicants and cardiovascular toxicants than cigarette smoking. These results are consistent with the epidemiology you've seen and together they provide a strong case for a decrease in individual risk for cancer, respiratory disease, and heart disease when smokers switched to Camel Snus.

Next, I'll summarize the findings from the preclinical studies which produced results consistent with the human studies and the epidemiology. Both animal and in vitro toxicology testing have been established for FDA oversight of different product sectors and have utility in the evaluation of

inherent toxicity of tobacco products. We conducted animal studies with the Camel Snus tobacco blend, which is the principle source of toxicants. The same blend is used in all six Camel Snus products.

We also conducted in vitro studies which include cytotoxicity and mutagenicity assays on all six Camel Snus products.

The preclinical studies chosen reflect standard testing methodologies in animals and in bacterial and mammalian cells. In the interest of time, I'll summarize the results from the animal studies and show you results from the cytotoxicity and mutagenicity assays.

Animal studies can serve as an important link between the epidemiological and clinical studies and the chemistry and in vitro results.

Neither subchronic nor chronic oral studies of rodents exposed to Camel Snus tobacco resulted in systemic or organ-specific toxicity or carcinogenicity at any time point.

Further, the hematology, clinical chemistry, and gross and histopathologic organ endpoints were all the same as controls.

Toxicokinetic evaluations of nicotine and cotinine levels in the animals confirmed that the highest dosages they received

far exceeded those typical of smokeless tobacco consumers. The snus results are in contrast to studies of rodents exposed to cigarette smoke.

Studies of cigarette smoke exposure showed histopathologic changes of the respiratory tract and compromised respiratory function, both of which are precursors to lung cancer and respiratory disease. Smoke exposure also showed significant elevations in markers of inflammation and oxidative stress, which are precursors to cancer, respiratory disease, and heart disease.

In addition, dermal exposures to cigarette smoke condensate induced significant malignant epidermal skin tumors.

Taken together, these results are consistent with the conclusion that switching to Camel Snus reduces the risk for lung cancer, oral cancer, respiratory disease, and heart disease.

Now let's look at the results from the neutral red assay, which assesses cytotoxicity. Cytotoxicity is characterized by impaired cell function or cell death and is caused by permeation of toxicants into the cell. It's associated with inflammation and irritation, which are implicated in the development of cancer, respiratory disease, and heart disease.

The cytotoxicity assay was conducted with all six variants of Camel Snus, which included all five flavors and both pouch sizes. All are shown on this slide in comparison to combustible cigarettes.

The bars show differences in cytotoxicity of Camel Snus extract relative to cigarette smoke. The results show that Camel Snus extracts, from all variants, are less cytotoxic than cigarette smoke. And the results are consistent across flavors and across all pouch sizes. These results are consistent with a reduction in risk for cancer, respiratory disease, and cardiovascular disease with Camel Snus use compared to cigarette smoking.

This slide shows the results from the Ames assay, which tests the ability of a substance to mutate individual genes. This is an important mechanism for cancer initiation.

Five salmonella strains of different genotypes were used in this assay, one of which is shown here. The results for cigarette smoke are the dose response curves in red and the results for the Camel Snus extracts are the lines in blue. And the results for all six variants are shown on this slide. The results show that cigarette smoke produces high levels of mutagenicity while Camel Snus extracts showed no mutagenic

activity. The slide shows compellingly that all Camel Snus products were similar. And taken together, this demonstrates that Camel Snus is less mutagenic than cigarette smoke. These results are consistent with a reduction in cancer risk with Camel Snus use compared to cigarette smoking.

And now to summarize the preclinical data, the results of subchronic and long-term rodent studies show that Camel Snus does not cause systemic or organ-specific toxicity or carcinogenicity at any time point, and the in vitro studies demonstrate that extracts of Camel Snus are less cytotoxic, less mutagenic, and less genotoxic than cigarette smoke.

The results are all consistent with the clinical studies that show convincingly that Camel Snus exposes individuals to significantly lower levels of carcinogens, respiratory toxicants, and cardiovascular toxicants than cigarettes.

Overall, the clinical and preclinical evidence is consistent with the epidemiology and taken together, they compellingly show that switching completely to Camel Snus from smoking presents individuals with less risk for lung cancer, oral cancer, respiratory disease, and heart disease.

And now Dr. Shiffman will talk about the risk perceptions, comprehensions, and likelihood of use studies.

DR. SHIFFMAN: Good morning. I'm Saul Shiffman, I'm an academic clinical research psychologist. I've been doing research on cigarette smoking and smoking cessation for some 45 years, 34 of those at the University of Pittsburgh. But I'm here today in my capacity as a consultant with Pinney Associates, through which I consult to Reynolds both on their smoking cessation products and on harm reduction products such as snus.

Now, you've already heard from the last two speakers about the evidence that shows that Camel Snus carries less individual risk of diseases, which supports the modified risk claims. What I'll describe is people's responses after seeing the particular ads. Specifically, I'll show you what the risk perceptions were after seeing the ads, how they understood the information, and perhaps most importantly, the likelihood of use of snus.

As you've seen, this is the modified risk advertisement. As Dr. Ogden mentioned, the ads were laid out to facilitate communication and their reading level tested at around the 7th grade reading level. Each of the advertisements was tested as a unified whole, firstly, because as you heard from Dr. Ogden, the intention is that these would be used as a whole and not in

any subparts, but also to be sure that people who viewed the entire ad came away understanding the key points after seeing both the modified risk information and the balancing information.

As you've already heard, there were three different executions or versions and here you can see again how the three differ in the key modified risk information. All three advertisements were tested in the same way and the results are largely similar. There just isn't time to present all detail on all three, so I'll focus on data from Execution 2 as an example, but as I go, I'll show you the data from all three executions so you can see how similar they are.

Now I'm going to frame each part of the research program in terms of the research questions for each. For risk perceptions, the question was "Do people seeing the ad understand that switching to Camel Snus carries less risk, but" -- very importantly -- "that it still has risk?" We don't want people to assume that there is no risk with the use of snus.

Now, in order to think about and evaluate the risk perception seen in the study, we have to keep in mind the backdrop of consumer misperceptions about the relative risk of

tobacco products and to address that, here are the data from an FDA paper based on the Federal HINTS survey where people were asked whether some smokeless tobacco products are less harmful than cigarettes.

Only 11% understood correctly that some smokeless tobacco products carry less risk, more than one out of five, 22%, didn't know, and fully two-thirds got it wrong and believe that it's not possible for any smokeless product to carry less risk.

So misperceptions about the relative risk of smokeless tobacco are highly prevalent and that's an important backdrop for the data I'll be presenting to you.

The data on risk perceptions and comprehension for Execution 2 were collected from roughly 5,000 individuals from online research panels. They were recruited according to their tobacco use status, the sample was diverse by gender, ethnicity, and education, and it was balanced and weighted to reflect the U.S. population demographically. The study was conducted by an independent research company, Naxion Research.

Participants saw the ad that you've seen, including one of the four mandatory smokeless tobacco warnings rotated randomly, and then they were asked to address the absolute and relative risks of smoking and Camel Snus, and they were asked of their

understanding of the issues covered in the balancing statements.

This approach follows the practice that FDA, on the drug side of FDA, recommends for evaluating over-the-counter drug labels, that is, participants view the information and their beliefs and knowledge are assessed.

The idea is that the public health concern is that people understand the important issues, not necessarily to discount that they may have already understood things before seeing the information and that logic applies here as well; indeed, the Center for Tobacco Products has pointed to the FDA's practice of OTC label comprehension as an example. In any case, I'll go through how the assessment was done and what the results were.

Turning to perceptions of relative risk, there are two ways to assess people's perceptions of risk, which I'll refer to as indirect and direct methods. We'll start with the indirect method which asks people to numerically rate the absolute risk of smoking and in this case, of Camel Snus, separately and we do the comparison, we compare the numbers to get at a relative risk. The direct comparison method asks people to directly make the comparison of relative risk and each of these gives us insight into risk perceptions. Both

types of questions were asked about each of the diseases mentioned in the modified risk information.

Let me start by showing you the absolute risk perception data for cigarette smoking. What you can see is that people do understand that cigarettes are very high-risk products. The ratings are all very high, near the top of the seven-point scale. People get that smoking carries high health risk and this was true for all four diseases.

Now let's look at the results for Camel Snus, which is shown here in the blue bars. You can see that they rated Camel Snus as lower risk, but certainly not no risk. In fact, all of the ratings for Camel Snus are above the midpoint of the scale, marked here by a line. So even though snus was rated as lower risk than smoking, people understood that snus was not without risk. In fact, even the epidemiology that you've seen, they actually are underestimating how much lower the risk of Camel Snus is compared to cigarette smoking.

I do want to point out one other thing. You'll notice that the relative risk reduction is smallest for oral cancer. When you saw the modified risk information, it doesn't differentiate among the four diseases but gives the same information for all four, that switching completely to Camel

Snus can reduce the risk of the four diseases.

So this suggests that respondents, the distinction they're making for oral cancer is coming from their preconceptions and intuitions about disease, the idea that if you put tobacco in your mouth it's bound to cause oral cancer. So this sort of natural misperception has been documented in published qualitative research.

The point is that some of the risk perceptions and relative risk perceptions are based on people's preexisting misconceptions and these are not instantly overcome by a single exposure to an advertisement from a tobacco company.

Going back to the overall direct risk comparison -- indirect risk comparison, you can see here the data for all three executions for the diseases in the modified risk statement. The previous slide was for Execution 2 and that's here as the middle set of bars with slight shading. You can see that the patterns -- from the patterns that the risk ratings across the three executions are very similar.

Now, besides assessing the risk for these specific diseases, we also assess people's risk perceptions of generally poor health, that's how the item was worded; results are very similar. As you can see here, people rated cigarettes as very

high risk and rated snus as lower risk, but certainly not no risk. Again, the scores are right above the midpoint of the scale.

Now again using Execution 2 as an example, let's look at the direct comparison of risk where people were asked to directly compare snus and cigarettes and the same way -- the risk of each disease is the same, less or no risk at all, which of course, would be the response of concern. I've combined here less risk in green and same risk in orange in the stacked bar to focus on the other two potential responses. There was only a small proportion, in red bars, who thought it had no risk at all, less than 10% in each case, and about 10% in the gray bars were not sure or didn't know, which is half of what we saw in the HINTS survey. So although some people were still unsure, this is much less than what we see in the general population.

And, indeed, the percentage who incorrectly thought that snus carried the same risk as smoking, in the orange box, was also cut by at least half compared to the population data in the HINTS survey. So people coming away with a more accurate understanding of the relative risk of smoking and Camel Snus.

And a key point is that people do not exaggerate the risk

reduction from Camel Snus; very, very few coming away thinking it has no risk.

And, again, if we look at all three executions, they are very similar. Across all three executions, across all diseases, few didn't know and few think there's no risk.

Another issue that was assessed was the idea that to get this benefit, smokers should switch completely and you can see this was generally well understood, about 80% got that right. Less than 5% thought you could add Camel Snus and get a benefit and about 18% were not sure.

And, again, these are roughly similar across the three executions. Most understood that smokers should switch completely to receive a health benefit.

The bottom line is that seeing the modified risk advertisement, people understood that Camel Snus has less risk than smoking, but certainly understood that it still has risk and they understood that smokers should switch completely to get that benefit.

The next part of the research was to test understanding of the balancing information; that is, the message is that even though Camel Snus has lower risk, that it has nicotine and is addictive, that nonusers of tobacco shouldn't start and that

the best choice for smokers is to quit completely.

Here you see the data. Over 80% were correct for each of those balancing statements and the incorrects were well under 10%. So the balancing cautionary information was well understood and yet again, this was similar across the three executions. The vast majority get the correct answer.

So people do understand that snus is addictive, that non-tobacco users shouldn't use it, and that the best choice for smokers is quitting.

But as important as it is to see that people understand this information, perhaps the most important thing is to understand who would use the product, because use by different subpopulations has different implications for population health.

Adoption by continuing smokers, by which we mean smokers who wouldn't otherwise quit, clearly would benefit their health and through that, the population's health.

But adoption, either by people who are not using tobacco or even by current smokers, if they would otherwise quit, has the potential to convey harm rather than benefit because although Camel Snus is less harmful than smoking, it still carries some harm, so it shouldn't be used by these groups.

So the purpose of the likelihood of use study was to understand the likely use in those subpopulations where a particular focus on seeing that the modified risk advertisement did not attract use from populations that shouldn't use the product.

So the question for the likelihood of use study was essentially, "Who will use this product?"

The sample assessing this for Execution 2 was again large, over 11,000 individuals, again covering the range of smoking and tobacco use behaviors, again diverse, again weighted to match the U.S. population, and again conducted by Naxion Research.

Now, in this study people were randomized to see either the modified risk advertisement that you've seen, containing both the modified risk information and the balancing information or a control ad that didn't have either the modified risk information or the balancing information and they were asked to indicate, in a quantitative way, their interest in using the product.

Now, their interest was expressed on a Likert scale from 1 to 10, but that itself doesn't yield an estimate of the probability of use. There's a big gap between saying on a

questionnaire that you're interested and actually going out and purchasing and using the product.

So how to turn a rating like this into a probability of use. Now, there's a common practice of simply taking scales like this and picking a threshold above what you say well, yeah, that indicates a likely user. A common example that you're probably familiar with is the use of a top two box rating on a five-point scale picking people who give the top two answers and asserting they would use the product. But any marketer will tell you that that is not a realistic estimate of who will use the product, it's an overestimate. Again, saying you're interested on a questionnaire is very different from going out and buying and using the product.

So we sought to use a method that would project the likelihood of actual use and to do so empirically. A longitudinal study was done and baseline, people made ratings like this for a tobacco product on a 1 to 10 scale and then they were actually followed 9 months later to see who actually bought and used the product.

The analysis resulted in a logistic regression equation to predict the actual use from ratings with demographics and tobacco use status as modifiers. That algorithm was applied to

the ratings in this study to generate a projected percentage who would likely use Camel Snus within 9 months and those are the data I'll be showing you.

Here are the data crucially broken out by key tobacco subgroups. These distinguish those who may benefit from switching to snus, smokers, and those who are currently not using tobacco, former and never users of tobacco, who should not start using snus or any tobacco product. The third bars are for the modified risk ad and the speckled bars are for the control ad. Notice, first of all, that among those who saw the ad, current smokers' likelihood of use is 20 times higher than that of the never users of tobacco, whose likelihood of use is projected at less than one-half of 1%.

And the current smokers projected -- sorry, current smokers' projected use is actually almost seven times higher than even former users of tobacco, and I will say that among the former users, there's a big difference between the stable former users whose likelihood of use is very close to the never users.

But if you look at the current users, you can see that they responded differentially to the modified risk ad over and above the control ad and, in fact, this is the only group that

showed greater interest than likely use when shown the modified risk advertising.

But now let's drill down on the current smokers. The data you've seen is for all smokers, but we've talked about the fact that we need to consider differently use of snus by smokers who are likely to quit versus smokers who are not likely to quit. So the data can be segmented based on expected quitting and this is based here on expected quitting in 9 months to match the time frame of projected use from the algorithm and let me show you those data.

At the top are those not expecting to quit and at the bottom, those who are expecting to quit. You can see the projected use is twice as high in those who are not likely to quit and therefore can benefit from switching to Camel Snus. And in fact, again, this is the only group that responds differentially to the modified risk ad. So the communication is reaching the intended target, smokers not headed to quitting.

And this is true in all three executions. The likelihood of use is highest among those not likely to quit. You can see that in Execution 1, the likelihood of use among continuing smokers is a little lower than in Executions 2 and 3, but in

all three executions, crucially, the likelihood of use is greater among those not likely to quit. So across executions, the communication is reaching the intended target, the smokers who have continued to smoke and can benefit from switching to snus.

Let's switch now to talking about initiation among those who never used tobacco. These are the data I've already shown you for the projected use of snus among never users of tobacco. And you saw the projected use was very low, less than one-half of 1%. But this is all ages and it's important to understand the likelihood of use among younger respondents, which is where initiation may be more of a concern. In a moment I'll show you data on the cohorts of these never users.

But also, just as with current smokers, we have to make distinctions and consider different subsets of the never users, in this case, individuals who might otherwise go on to smoke versus those who would not, and this was measured by using the well-known scales developed by John Pierce for smoking susceptibility.

So here's what the data looked like. This is for a young cohort ages 18 to 22. You can see that overall projected use among never tobacco users is still very low, even the highest

group is only at about 1%, but this is the line with the people who are susceptible to smoke, that is, who might be going on to smoking.

And if they're headed to smoking, adoption of a lower-risk product may well be a benefit to them and to the population, while among those who are not headed to smoking, you can see that the projected use is very low, less than one-quarter of 1%. In fact, you can barely see it, but it trends lower among those who saw the ads, perhaps because of the cautions in the balancing information. But the point is that these data are very reassuring about the potential for initiation with Camel Snus with modified risk information.

And the patterns are, again, similar across executions. About 1% or less among those susceptible to smoking and about one-quarter of 1% among those non-susceptible. Across executions, this is reassuring about any potential risk of initiation with Camel Snus.

Now, what we've walked through suggests a way to summarize the data, which you see here for all three executions. This contrasts the group who could most benefit from switching to Camel Snus, continuing smokers, in green, and the group, in red, that one most wants to make sure do not take up Camel

Snus, the individuals who have never used tobacco or anyone susceptible to smoking.

And you can see that for all three executions, use by continuing smokers is projected to be 20 to 30 times higher than use by non-susceptible never users, whose projected use is about one-quarter of 1%.

This framework or this contrast between these two populations gives us a useful lens through which to also examine the data from important subgroups and I'll show you two breakouts, by gender and by ethnicity.

Here are the data by gender. You can see that the results hold up well for both men and women. Currently, 20 to 25% of snus users are women, but these data suggest that giving female smokers, especially continuing smokers, accurate, relative risk information may stimulate more interest. And in both genders, use by never users is very unlikely.

This shows the data for non-Hispanic Caucasians, non-Hispanic African Americans, and Hispanic Americans. You can see that the -- in the intended group for harm reduction, smokers not likely to quit smoking, there is actually more interest among African Americans and especially among Hispanic Americans, where there's more than a 6% increase in response to

the modified risk ad. So the message has appeal in these important subpopulations.

But in all groups, interest is higher among smokers not expecting to quit, some 30 times higher than among never tobacco users where there's almost no interest or projected use. So this dynamic holds across gender and ethnicity.

So the likelihood of use data show that across all three executions and for a number of important subpopulations, the modified risk information generates the most interest and the greatest likelihood of use in the populations who can most benefit, smokers who are going to continue to smoke.

And, in contrast, it gets much less interest from former tobacco users and almost no interest from people who aren't already tobacco users.

In summary, after seeing the modified risk ad, people understood that Camel Snus has lower risk, but that it's not risk free. People also understood key cautionary information.

And the modified risk ad generates, by far, the most likelihood of use in the people who can benefit, that is, continuing smokers.

Now, this research on likelihood of use evaluated the likelihood of use in these important subpopulations. The task

of statistical modeling, which you'll hear about shortly, is to integrate these patterns of use to estimate the net impact on population health. But even before we get to the formal modeling, given what you've heard about the epidemiology and toxicology, given what you've heard about the use in these different subpopulations, I think the data already make it apparent that Camel Snus, with modified risk information, is likely to benefit the population's health.

And with that, I'm going to turn it over to Dr. Curtin to present the formal model.

DR. CURTIN: Good morning, my name is Geoff Curtin, and I'm the Senior Director in the Scientific and Regulatory Affairs group at RAI Services Company.

As noted by Dr. Ogden, FDA may issue a risk modification order after determining a product will significantly reduce individual harm and the use of that product would likely benefit the health of the population as a whole, taking into account tobacco users and nonusers.

To that end, my colleagues have presented considerable evidence demonstrating that the health risks associated with using Camel Snus are significantly reduced compared to smoking, and that the proposed modified risk advertising differentially

appeals to those most likely to benefit from using Camel Snus, that is, continuing smokers.

Now I'll present results from our multiple cohort modeling used to assess the overall population health effect of advertising Camel Snus as a modified risk tobacco product.

Our modeling integrates empirical probabilities for the use of Camel Snus by key subgroups of a population that is mixed in terms of age, gender, race, ethnicity, and tobacco use status, and assigns mortality risk based on the product that's being used and its duration of use. As you will see, the modeling accounts for both the potential benefits and harms from using Camel Snus, and estimates the effect on mortality for the population as a whole.

I want to emphasize a couple points about the modeling. First, the modeling I'll describe accounts for a wide range of use patterns among different tobacco user groups and at different points in their lifetime. And second, modeling is best suited for estimating trends and likelihoods rather than predicting exact numbers.

That said, the modeling projects about 350 to 450,000 additional survivors for the full population across the three advertising executions. But it really is the direction and the

magnitude of this projection that gives confidence that Camel Snus, with its proposed advertising, is expected to benefit the health of the population as a whole.

So I started by providing an overall projection from our modeling. Now I'll show you why there's good reason to have high confidence in a population health benefit.

First, our model was validated by faithfully reproducing actual population mortality statistics, in particular, U.S. and Swedish life tables, to within less than 1%. This validation was peer reviewed and published in 2013.

Next, our modeling accounts for all harmful changes in tobacco use that may occur for Camel Snus, including never tobacco users initiating with snus and subsequently transitioning to smoking, and current smokers being diverted from quitting.

Our modeling relies on empirically derived inputs including probabilities of use for Camel Snus, as were just described.

And, finally, our modeling is supported by sensitivity testing of the primary inputs, those with the greatest potential to affect the projected benefit. I'll spend just a couple minutes discussing each of these features.

The model used for our analyses is a dynamic population modeler developed by Ramboll. This modeling uses a core framework to compare the projected number of survivors for two scenarios, a "what currently is" scenario or simplified base case that also allows use of cigarettes, and a "what could be" scenario or counterfactual that also allows the use of snus.

The model tracks all-cause mortality for each scenario through age 102 and then contrasts the number of survivors across multiple 5-year age intervals through age 72. Beyond that point, age-related mortality begins to obscure smoking-related mortality.

For the "what currently is" scenario, each cohort may transition to or from smoking at each 5-year age interval, and for the "what could be" scenario, each cohort may additionally transition to or from snus at that same interval.

As I mentioned earlier, our modeling accounts for a wide range of use patterns among both tobacco users and nonusers, and assigns risk, mortality risk, based on the product that's being used and its duration of use.

First, I'll explain the changes in use patterns for never tobacco users. We start with a population of never users ages 13 to 17 and based on empirical transition probabilities for

the "what currently is" scenario, these never users are either headed to smoking or not headed to smoking.

For those never users who are not headed to smoking and do not initiate the use of snus, they remain never users but may change their use patterns during subsequent age intervals. If instead these never users initiate the use of snus, they begin to incur the harms of using the modified risk product. Additional initiation is the first of six harmful transitions accounted for in this modeling.

The next possible transition for these snus initiators considers whether their use of snus directly leads to smoking. For those snus initiators who do not transition to smoking for the duration of the follow-up, they remain snus users. This is because in the absence of empirical estimates for Camel Snus quitting, we adopted a conservative approach of not accounting for this beneficial transition in any of our modeling. For those snus initiators who do transition to smoking, they begin to incur the full health risks of being a smoker.

Gateway potential, a gateway effect, has the potential to substantially harm the health of the population because of its effect on individual health. In the absence of empirical estimates for transitioning from Camel Snus as a modified risk

tobacco product to smoking, we adopted hypothetical conservative probabilities of 50%.

For those never users who are headed to smoking and do not initiate the use of snus, they proceed as they would have in the "what currently is" scenario and begin to incur the full health risks of being a smoker. If, however, these projected smokers instead initiate and continue to use snus, they're diverted from the full health risks of smoking. Alternative initiation is one of only two beneficial transitions accounted for in our modeling.

There is the potential that some of these snus initiators will subsequently transition to smoking. Delayed smoking would not introduce additional harm to the population, as these individuals were already headed to smoking. Instead, this transition reduces the benefit expected from alternative initiation.

The right half of the schematic is used to show tobacco use patterns for those individuals who have already become smokers. Again, based on empirically derived transition probabilities for the "what currently is" scenario, these smokers are either headed to quitting or not headed to quitting. For those smokers who are headed to quitting and do

not adopt the use of snus, they transition to abstinence for the duration of the follow-up period.

For those smokers who are headed to quitting but instead adopt the use of snus, they're diverting from and thus lose the benefit of complete quitting. The harm incurred for these individuals has the potential to be further increased if adoption of snus then leads to the relapse to smoking.

For those snus adopters who do not relapse to smoking for the duration of the follow-up, they remain snus users. If, however, some of these snus adopters are caused to relapse to smoking, they return to incurring the full health risks of being a smoker. The effect of relapse was examined during sensitivity testing and accounts for the potential harm incurred by former smokers who, having adopted snus, return to smoking.

For those smokers who are not headed to quitting and do not adopt the use of snus, they proceed as they would have in the "what currently is" scenario and continue to incur the full health risks of smoking. If, however, these continued smokers instead switch completely from cigarettes to snus, they have the potential to significantly reduce their individual health risks. This beneficial transition of switching is the intended

behavior for Camel Snus and its proposed modified risk advertising.

Finally, our modeling considers that some of these snus adopters may return to smoking. Because these individuals would've continued to smoke, inclusion of resumed smoking serves to reduce the population health benefit expected for switching.

So we've accounted for all harmful changes in tobacco use that may occur for Camel Snus, six in total, and the modeling projects substantial increase in survival for the population as a whole, including tobacco users and nonusers.

This chart compares the magnitude of effect for each of the transitions I just described, presented as a percentage of the effect of switching. Beneficial transitions are displayed as projecting to the right and harmful transitions to the left. Solid bars represent primary transitions to snus and the slashed bars represent secondary transitions from the use of snus to smoking, which either mitigate the effect of a beneficial transition or elevate the effect of a harmful transition. For example, resumed smoking dramatically reduces the expected beneficial effect of switching.

What's obvious from this chart is that the transition with

the greatest effect on population survival, as projected empirically from the likelihoods of use testing described by Dr. Shiffman, is continuing smokers switching to snus. In contrast, the harmful transitions for initiation or adoption of snus have a much smaller effect. This is why the overall population health effect for Camel Snus is projected to be beneficial.

Another reason for high confidence in the projected population health benefit for Camel Snus is our use, to the extent possible, of empirically derived inputs. I'll just point out a few that are of particular importance.

First, for the expected reduction in mortality when switching from smoking to snus, we used consensus estimates provided by Levy et al., based largely on the same epidemiological evidence presented by Dr. Marano and included in our application. An expert panel estimated that the reduction in all-cause mortality risk for snus compared to cigarettes is at least 89%. All the modeling I'm presenting today is based on an 89% reduction in risk for Camel Snus.

It also bears mentioning that dual use of snus and cigarettes was assigned the same high risk as continued smoking in our modeling, consistent with information provided by

Dr. Round showing that dual use does not increase exposure to harmful chemicals.

Also central to our modeling estimates or inputs for the use of Camel Snus, transition probabilities for the "what could be" scenario were derived empirically from the likelihoods of use testing discussed previously by Dr. Shiffman. That testing provided age interval-specific probabilities for key subgroups of the population, including continuing smokers, who are the intended audience for the advertising, and nonusers of tobacco.

There were a few transitions that were difficult to estimate based on consumer testing because they involve a second step after adopting snus. In effect, we'd be asking the individuals whether the use of snus would then cause them to begin smoking.

As previously discussed, we adopted hypothetical conservative probabilities of 50% for these harmful transitions. For example, we assumed that fully half of those never tobacco users, who would've remained never users and instead initiate use of snus, were then caused to take up smoking.

Given the importance of both the transition probabilities for use of Camel Snus and the expected risk reduction for snus

compared to smoking, we conducted sensitivity testing. For example, we considered that the actual probabilities for using Camel Snus might be lower than what were projected empirically.

Sensitivity testing showed that reducing these probabilities by 75%, including those for switching, while retaining the harmful transitions from snus to smoking, still provided a substantial benefit of about 95 to 120,000 additional survivors across the three advertising executions.

This means that the survival benefit would be retained if the empirical projections for switching, which had already been reduced by half due to resumed smoking, were further reduced by three-quarters. In effect, the use of switching probabilities that were only one-eighth of what was projected empirically still yields a substantial population health benefit.

We also conducted sensitivity testing for the expected risk reduction for snus compared to smoking and found that even if the estimated risk reduction was as low as 53% and not the estimated 89% provided by Levy et al., there would still be a projected benefit.

So what I've shown you today, what statistical modeling demonstrates is that the proposed modified risk advertising for Camel Snus is expected to result in an overall benefit to the

health of the population as a whole.

And there's good reason to have a high confidence for a projected population health benefit based on our use of a validated model that accounts for all unintended harmful changes in tobacco use using, to the extent possible, empirically derived model inputs which were then subjected to sensitivity testing.

Based on empirical probabilities for use of Camel Snus by tobacco users and nonusers, our multiple cohort modeling projects an estimated 350 to 450,000 additional survivors for the population as a whole. This range reflects projections across the three advertising executions.

It is the magnitude of this projected benefit and its persistence during sensitivity testing that makes it highly likely that Camel Snus with modified risk advertising will benefit public health.

I'll now turn the podium over to my colleague, Dr. Ogden, to provide a summary of today's presentations.

DR. OGDEN: Thank you, Dr. Curtin. And I'd like to thank the Committee for giving us this opportunity to summarize the extensive body of scientific evidence that supports the modified risk advertising applications that we filed for Camel

Snus.

As you heard this morning, there's clear, consistent and compelling evidence that marketing Camel Snus as a modified risk tobacco product will not only benefit individual adult smokers, but will also have a net positive impact on U.S. public health.

In particular, we've highlighted an extensive body of scientific evidence demonstrating that smokers who switch completely to Camel Snus can greatly reduce their risk for lung cancer, oral cancer, respiratory disease, and heart disease, and that there's a high likelihood that authorizing the proposed modified risk advertising for Camel Snus will result in a significant net health benefit for the population as a whole.

Our confidence in these conclusions is bolstered by the results of consumer studies, which indicate that the advertisements we have proposed offer smokers accurate information on which they can base decisions to mitigate their risk.

Along with that education, the ads communicate important balancing information, that no tobacco product is safe and Camel Snus still presents some risk, that Camel Snus is

addictive and that the best option for smokers is to quit completely.

Testing confirmed that the ads appealed most to those individuals who would benefit most from using Camel Snus, that is, smokers who are not likely to quit. And in comparison, the likelihood of use among former smokers and never smokers was very low.

One last thing before I present our overall conclusion. I mentioned this in my introduction and I believe it bears repeating before we begin our Q&A.

If the FDA grants authorization for modified risk messaging for Camel Snus, we will work with the Agency to develop and implement a robust postmarket surveillance program that monitors a wide array of relevant information sources, including government agencies, consumer call centers, and such resources as the PATH Study, the Monitoring the Future Study, the National Adult Tobacco Survey, and the National Youth Tobacco Survey, to name just a few.

We will immediately report any unanticipated or unfavorable information to the Agency as soon as we become aware of it, and we will file annual postmarket surveillance reports with the FDA as required by the Tobacco Control Act.

I'd also like to point out that there are additional safeguards built into the process, including FDA's ability to rescind MRTP authorization if warranted, and the fact that MRTP authorization is not permanent but must be reauthorized after a period of time that will be designated by the FDA.

In terms of the Tobacco Control Act requirements, Section 911 requires that a significant harm reduction be shown for both the individual and at the population level using scientific methods and standards listed on this slide. The extensive scientific evidence we submitted with our applications and the summaries we presented today fulfill these requirements for Camel Snus.

I want to wrap things up by noting that the facts that we presented today, backed by the enormous body of research that we submitted to the FDA in support of our modified risk applications, clearly demonstrate that authorizing the proposed modified risk messaging for Camel Snus is a strong, scientifically sound step to reducing the harm caused by cigarettes for individuals as well as for the population as a whole.

Taken together, the data show that communicating the modified risk status of Camel Snus as an MRTP will benefit

population health.

And should we receive the modified risk tobacco product order, there will be responsible communication of this new information to smokers. And under the direction of FDA, we will develop and implement a robust postmarket surveillance program.

Now, as I mentioned, we've asked Dr. Shiffman to moderate the question and answer session. And along with the speakers who you've heard from already, we have a number of additional subject matter experts available to help answer your questions.

And now Dr. Shiffman.

DR. MERMELSTEIN: Before we begin, Dr. Shiffman, I am aware of the time and sometimes people's need for a break. So why don't we start, but I'm just giving a warning that I'm sensitive to a break and balancing the need for pressing questions as well as perhaps a break and coming back to finish, so let's -- we'll start.

DR. SHIFFMAN: Of course. I don't think we want hungry speakers out there.

DR. MERMELSTEIN: Right, but thank you, Dr. Ogden, and thank you and your team for a clear set of presentations and --

DR. SHIFFMAN: And let me just mention first, as we get

started, you may be distracted by these folks back here with headsets. Those of you on this side may even hear them whispering. They're just trying to help us find slides that would help us answer your questions and communicating with the guy at the end who actually is able to show the slide. So pay no attention to the people behind the curtain.

DR. MERMELSTEIN: Okay, thank you. We're going to start with a question from Dr. Thrasher on the phone.

DR. THRASHER: Hi, thanks. This is a question for Dr. Marano. On Slide CC-31, some of the epidemiological data around oral cancer were presented showing that smokeless tobacco users have about the same risk of oral cancer compared to nonusers of tobacco and I guess I'm struggling a little bit with squaring those data with the information as presented from the U.S. Surgeon General's report saying that smokeless tobacco is associated with oral cancer.

So can you help me understand why the data that are presented show no risk and then the U.S. Surgeon General says that there is risk?

DR. SHIFFMAN: I'll ask Dr. Marano to respond in a moment, but it's essential to remember that what's before the Committee today is the relative risk relative to smoking, that Reynolds

is not proposing to remove the warning that says that it may cause mouth cancer, so it's really the relative risk. But as to your particular question, let me ask Dr. Marano to respond.

DR. MARANO: And just to reiterate, this is one study, CPS-II, which is a very large cohort, conducted in the United States by the American Cancer Society. But let me show you some additional data on oral cancer which I think will help answer your question. Can I have Slide 2, please?

So these are some additional data on oral cancer. At the top of the figure you'll see data on smokeless tobacco and at the bottom of the figure you'll see additional data on cigarette smoking. And, again, as Dr. Shiffman mentioned, the claim is really about smokeless tobacco relative to cigarette smoking.

So what you'll see for smokeless tobacco, the data show, generally, risk estimates hovering around one, and you will -- and these are data from the U.S. and Sweden -- estimates hovering around one. You do see some outliers but again, based on the totality of the evidence, smokeless tobacco is much, much lower than cigarette smoking.

There are some estimates from meta-analyses in there; hopefully you see those designated by meta-analyses, meta-

analyses by Boffetta and Lee and Hamling. Probably you're well aware that those groups of studies -- overall estimates. I hope that answers your question.

DR. MERMELSTEIN: Thank you.

DR. THRASHER: Thank you, yes.

DR. MERMELSTEIN: Dr. Bierut.

DR. BIERUT: Thank you. I'm trying to get a perspective of the additional survivors in the modeling and its reported 350,000 to 450,000 saved lives. Over what time period is this occurring?

DR. SHIFFMAN: So I'll ask Dr. Curtin to explain that, but briefly, remember that we're following -- the model follows people, including a very young cohort, out to age 72, but Dr. Curtin can say more.

DR. CURTIN: Yes. So the period we're talking about in the modeling is a period over 55 years. So the multiple cohort modeling is made up of a series of 5-year age groups that represent the full population and is mixed in terms of age, gender, tobacco use statuses. All the cohorts in this population are followed through age 72. The younger cohorts would be followed 55 years. Obviously, the older cohorts less time.

DR. BIERUT: So just to try to help me, again, put this on a yearly -- you know, I know that the modeling is complex, but 8,000 lives saved a year? Do you think the benefit accrues more over time?

DR. CURTIN: Yeah. So much like the reason it takes so long -- 55 years are in the modeling -- is the latency period for many of these chronic diseases, so you can't have the benefit right away. In the model, much like we'd see in the population, even with something like just cessation, you have much more of a benefit in the younger cohorts than you have in the older cohorts.

So what we see is, out of that projected benefit, about 130,000 additional lives are in that youngest cohort and smaller numbers as you get older. So it really is over that period of time with the younger cohorts bringing the biggest benefit because older cohorts have incurred some level of smoking-related disease, so there'd be less benefit there.

DR. MERMELSTEIN: Dr. Blaha.

DR. SHIFFMAN: Let me just add that there's another element which is remember that the model counts survival to age 72, so even if you were helped at age 40, it's not counted until age 72. That also delays the counting of those benefits.

DR. BLAHA: Hi, Mike Blaha. I have a clarifying question and then an observation regarding the modeling again, in particular, the sensitivity testing. So I appreciated the sensitivity testing, but I have further questions about it.

In particular, I'm interested in the phenomenon where someone who's a never tobacco user, a non-tobacco user, and takes up snus as their primary tobacco product, like we know potentially happens with other novel tobacco products. Well, I understand the comment that the relative risk of that is low. Of course, the absolute numbers may be high because the never tobacco-using population is the biggest population, for example, with electronic cigarettes, while the never using tobacco users who will take up these is a small percentage of these users. The absolute numbers are in the millions, right, of sole electronic cigarette users.

So my question is did you do a sensitivity analysis or can you present a sensitivity analysis where, for example, the potential for sole snus use is increased and does that have an effect on the total overall numbers of lives saved, etc., from the modeling exercise?

DR. SHIFFMAN: So to be clear, the modeling does explicitly take into account --

DR. BLAHA: Correct.

DR. SHIFFMAN: -- the size of that population as well as the probability.

DR. BLAHA: Right, sure, but small number of changes in the relative risk of sole snus use could have an outsized impact because of the numbers. So my question is -- I didn't see sensitivity analyses for that statistic.

DR. SHIFFMAN: Dr. Curtin.

DR. CURTIN: So if we could have the three-dimensional tipping points? So yes, we did do sensitivity testing, I did show some of that. We've got a slide on -- the model's able to do multi-dimensional tipping point analyses and so we have some examples of the impact. We increased the additional initiation as well as combine it with gateway and it will just take us a minute to show that slide. So if I could have Slide 3, please?

One of the strengths of the model is the tipping point analyses. The way we read this is the probability for additional initiation, which you heard from Dr. Shiffman on likelihoods of use testing, and what we modeled was about 0.3%, so that's all the way over to the left. And what we had in the model was about a 50% gateway effect. So that percentage of switching needed to offset that in a tipping point analysis is

about 2.25% across the whole population.

What this shows you is as you increase the probability of additional initiation from 0.3 to, let's say, 1.5, which would be five times that, and you cross it with the Y-axis which is probability of gateway effect, the contour lines tell what level of switching you would need to completely offset that to get a benefit. So that gives you some context. The reason why, at least at the 0.3, the low levels, you can see it really doesn't matter if you're 50% gateway or 100% gateway because you've got so few people moving, even recognizing what you brought up, it is a very large population.

DR. BLAHA: So let me just clarify. So the X-axis here is the probability, I'm going to call it, of sole snus use, snus use as the original tobacco product, right, that's the X-axis?

DR. CURTIN: Well, yes, but as we talked about -- Dr. Shiffman presented, there's people that are likely or susceptible to initiate smoking and people that are not susceptible.

DR. BLAHA: Okay, so there's other factors. Yeah, so just so I can interpret, I guess, for maybe the record. So if the probability of additional initiation is 1%, right, and the probability of a gateway effect, just so I can determine a

number, is 90%, that would be a tipping point --

DR. CURTIN: That would be a tipping point, and it would suggest that --

DR. BLAHA: It could potentially be harmful if those numbers are exceeded.

DR. CURTIN: So if you were just taking additional initiation and gateway together --

DR. BLAHA: Right.

DR. CURTIN: -- and that's all you were looking at --

DR. BLAHA: Correct.

DR. CURTIN: -- you would have a harmful effect.

DR. BLAHA: Right.

DR. CURTIN: It takes about 1% switching to completely offset that.

DR. BLAHA: That's very helpful. Thank you.

DR. SHIFFMAN: I think it's worth emphasizing again, Dr. Curtin said this, but I want it not to be lost, that the 50% gateway that was used in the model is very conservative because even putting aside that some of the people who do progress to smoking may have been headed to smoking anyway, the data show that the transition probabilities from smokeless to smoking are actually lower than that, even on an absolute

scale, even forgetting the fact that some of those individuals would've smoked anyway. So as is done in sensitivity testing, the modeling -- model extreme things that won't happen and I want to be sure we're clear where reality is.

DR. MERMELSTEIN: Dr. King.

DR. KING: Yes, thanks. So I have a comment that I'm sure is going to transform into a question. So I would like to bring us back to this issue of dual use, which I think is quite important and it's primarily in the context of the purview of this Committee and it's really as it actually is used by consumers and I think that's a very important, you know, qualifier.

And a lot of times, even with things like nicotine replacement therapy, you know, things go really well in randomized clinical trials, but then once it gets out into the population, things aren't always as well as we believe they would.

And that being said, I think it's very useful to see the epidemiologic data at the onset from CPS, albeit it's among men only and it's very old.

I do want to question the inclusion of some data on dual use and I would assume that it would be available, but I'd be

very interested in seeing, you know, what are those risks of mortality, specifically among dual users? And I do understand that dual use could be a means to an end, but nonetheless, you know, what is the effect of the mortality risk estimates among dual users that would presumably be available from that research? And if it's not available, you know, why not and what are the potential implications in terms of increased risk for, you know, the various considerations to that?

DR. SHIFFMAN: I think there are at least two questions in there, so --

DR. KING: And also one added is what is your understanding of the prevalence of dual use?

DR. SHIFFMAN: That makes three.

DR. KING: Yeah, three.

DR. SHIFFMAN: Let me ask, first, since your primary question was about epidemiology, to ask Dr. Marano to present data on dual use.

DR. MARANO: There are data on dual use, so let me show you some data on dual use. If I could have Slide 2, please? So these are some oral -- data on oral cancer for dual use. You can see dual users are the purple dots and exclusive smokers are in red. So what we see for dual use across the

board is no increased risk among dual users compared with exclusive smokers.

Can I see Slide 3, please? These are data for myocardial infarction. The top half of the figure are any myocardial infarction or nonfatal and at the bottom we see fatal myocardial infarction. I understand it's a bit crowded, but again, dual users are purple, paired with exclusive smokers in red and again, the conclusion that we can make here is no increased risk among dual users compared with exclusive smokers.

DR. SHIFFMAN: Okay. So you asked an epidemiological question, which I think Dr. Marano has addressed. Let me address your other questions and I'm going to take those, if you will, as a two-part question.

One is what is the prevalence? And in fact, there are -- there are several published estimates from population studies. They all hover at around 50%. This is for smokeless users. Some of them are for snus, but -- so Shu-Hong Zhu has estimated it at 53%, a paper by Chang coming out of PATH estimates it at 48%, and a paper by Sung, also from the National Adult Tobacco Survey, estimates it at 52%. So it's about half.

If you start to consider other products other than smoking

and smokeless, the figures are higher because, as several papers have shown, poly use is getting very, very common even among smokers, something like 40% are using another product. If you introduced another concept, which I think is very important, which is the idea that dual use is a transitional state and in fact, much as for those of us who've fought the wars on getting people to use nicotine replacement, that often there is a period of dual use as people transition to abstinence and you see very similar results even when you look, for example, at Slide 2, please.

So these are data from some of the studies. Slide 2, please. So these are three studies that actually estimated the transition probabilities from dual use to exclusive use and what you see is that there is -- it's much more likely that you get to exclusive use of a smokeless product through dual use, that that is the pathway. Some people do go directly from smoking, completely switching with no transition, to exclusive use of smokeless, but the majority of smokeless -- the majority of people who transition from using smokeless to exclusive dual use do so through dual use.

The other data that suggests that it's a transitional or unstable state is that, well, you might worry that dual use

leads people to kind of be complacent. In fact, what you see in those groups is that they're making quit attempts. And if we have the slide, I think it may be from Shu-Hong Zhu's study that shows the actual transition probabilities directly. No, not that one. Like I said, we have people trying to find the slide so we can show you data. No, the one, please, from -- but let me tell you what it will show, which is that people do make transitions from using smokeless -- sorry, from smoking to using smokeless and that the majority of those actually go through the pathway of dual use.

So we shouldn't think of dual use as a perpetual state but rather as a transitional state and for that reason, it's very reassuring that both the biomarker data and the epidemiology show that that state does not add to risk. We're not finding that slide, but I think I've told you what it would have said, so we'll move on.

DR. MERMELSTEIN: Dr. Weitzman.

DR. WEITZMAN: So I have a couple of comments and then a couple of questions. The first is that the conditions of concern that you speak about with benefits of advertising are not diseases, they're categories of diseases. There's not a single one of those that is a single entity, so I'm not sure

how that plays into this.

You also this morning presented mortality data, not morbidity data, and I'm not sure how important morbidity data is in our deliberations.

And then I have two questions. How were the conditions chosen? There are many other untoward consequences of exposure to tobacco products. And all the mortality data that you presented, I'm interested to know if those are adjusted analyses or bivariate analyses where you compare tobacco to Camel Snus.

DR. SHIFFMAN: I counted four questions or, at least, topics that I think we'll actually address.

DR. WEITZMAN: Right.

DR. SHIFFMAN: Let me start with the next to last one, which is how these were chosen. So if you think about it, cancer and respiratory disease and heart disease are by far the three leading causes of smoking-related deaths, so they became compelling ones for the claim.

Oral cancer is in there because, what you see in the data, I showed it to you, even in data after people are exposed to modified risk claims, is that there's an intuitive and incorrect belief that that's going to actually have more risk

than smoking. People forget that you take smoke through your mouth, so you actually have exposure to all of those combustion products. So it was considered important to add that, as well, for people to have a sense that this could be a safer product for them. So that's how those were chosen.

You asked two other questions. Well, one wasn't a question, but I think we need to address, which is these composites of diseases.

DR. WEITZMAN: Right.

DR. SHIFFMAN: And I'm going to ask Dr. Marano to explain what diseases are in there. That's how epidemiology usually does it, is by looking at outcomes.

And then a further question you had was -- two more, whether those estimates are adjusted and finally, data on morbidity. So I will try to keep track and make sure we get to your questions, but I'll ask Dr. Marano to kick off and I will punt to her if we don't get to all of them.

DR. MARANO: I'm going to start with what I think is the easiest one, the adjustment. So as much as -- the best of my recollection, multivariate analyses we took as the most adjusted analyses as much as possible.

The second easiest one, I believe, is incidence versus

mortality. The Swedish data that we presented today for lung cancer and oral cancer were actually incidence data, but I can show you some additional incidence data. Well, let me ask -- let me answer the other data -- the other question, I'm sorry. But can you rephrase that question or repeat that question, because I'm not sure I understood that.

DR. WEITZMAN: It is what diseases that are composites, what diseases were counted as respiratory --

DR. MARANO: So I think lung cancer, then, is the easiest, right? So bronchus, trachea, right? So then, for respiratory disease, mainly COPD, that's what we were focused on. Some studies, it was a conglomerate of respiratory diseases. The more robust studies had ICD codes. For coronary heart disease, I believe that's ICD Code 410 to 414. Some of the Swedish studies, it was just MI. So they were looking at hospital records, so they just -- whatever the doctors coded as MI, that's what it was. It just kind of depended on the study.

DR. WEITZMAN: It's mortality there, correct? Not just morbidity.

DR. MARANO: It depended on the study. There was both morbidity and mortality. I can show you some -- I can show you some -- we have plots just on incidence data, let me show you

some of that. But the lung cancer and oral data from Sweden that I showed earlier, that was incidence data.

DR. WEITZMAN: And how are you equating incidence data with my question about morbidity? How do those two relate? Incidence, to me, simply means the onset of a particular issue.

DR. MARANO: So the incidence of lung cancer, so --

DR. WEITZMAN: But some people live with lung cancer and there are multiple, multiple types of lung cancer.

DR. MARANO: Right. So they were living with lung -- so lung cancer occurred and they were living with lung cancer.

DR. WEITZMAN: You're saying that the difference between the incidence and the mortality data is what you're referring to as morbidity data?

DR. MARANO: Yes.

DR. WEITZMAN: Okay.

DR. MARANO: Does that answer your -- does that --

DR. WEITZMAN: I understand your reasoning.

DR. MARANO: Okay.

DR. WEITZMAN: I'm not sure I agree, but I understand how you got to that. Thank you.

DR. MERMELSTEIN: We can move on. We can do a couple people on the phone and then back to the Committee.

Dr. Giovino?

DR. GIOVINO: Yeah, hi. I have a couple questions that are more questions of clarification. I think the first one is for Dr. Marano and I'm interested in Slide CC-39 and CC-40. I did compare the PFNA levels in studies with brands much earlier and then current Camel Snus from the literature and current Camel Snus from RJR.

On Slide 39 it says that the constituent level in nanograms per grams of tobacco wet weight for products -- well, all the products on the slide range from about -- it looks like about 1.5 to 68 or something like that.

On Slide 40 it says constituent levels, nanograms per gram tobacco weight, wet weight, ranges from 1500 to 49 -- 5,000, whatever.

I got a feeling it's just a labeling problem, but we're talking orders of magnitude here and I just wanted to be sure I got my head wrapped around this slide correctly.

DR. SHIFFMAN: Dr. Marano, I think there is an issue of dry weight versus wet weight.

(Off microphone response.)

DR. GIOVINO: But they both say wet weight.

DR. SHIFFMAN: Yes, we put that there just to see if you

were paying attention, Gary.

DR. GIOVINO: Okay.

DR. SHIFFMAN: No, I believe -- well, I'm not sure which is which, but there's definitely a difference and it's because it happened that the Swedish data were measured in a different way than the American data. So apologies, there does appear to be a labeling change. I'll ask Dr. Marano to clarify that and we'll come back to you when we can --

DR. GIOVINO: Okay.

DR. SHIFFMAN: -- give you a clearer sense.

DR. GIOVINO: Thank you very much, Saul. My second question is for you, Saul. In the slides you presented where you compared the information on people's perceptions of, you know, relative harm and absolute risk and you compared it with HINTS. You know, you used HINTS as sort of the standard and, you know, part of me is wondering why didn't you just do an experiment with your own data, why didn't you just do another, you know -- another cell in your own survey so you could get a comparison instead of with the HINTS, using the HINTS data?

DR. SHIFFMAN: Well, the idea here is what we need to know is not so much what the experimentally demonstrated effect of the ad is, it's what do people believe after seeing the ad.

And from my perspective, frankly, particularly on the issue of risk perception, the thing that I was on the lookout for is having presented data that Camel Snus has less risk, would that lead people to conclude that it had no risk.

I think you know I published a study on some claims years and years ago that showed that that happened and in fact, what we see is that it's not happening, that if you look at the risk estimates after seeing the ad, people had very high risk ratings for Camel Snus, higher than the epidemiology would indicate. And they are, on this one to seven scale, in the range of five to six, nothing like --

DR. GIOVINO: Yeah.

DR. SHIFFMAN: -- an indication that they come away thinking it has no risk. So in my view, the data demonstrate that the advertisement does not mislead people into thinking that Camel Snus has no risk and that was, for me, a crucially important thing to demonstrate.

DR. GIOVINO: Yeah, I understand that too. Okay, thank you.

DR. MERMELSTEIN: Okay, one more from the phone and then we will just wrap up before lunch from a couple other -- I tracked them, but we'll take a break, okay.

So Sally on the phone, Sally Herndon.

MS. HERNDON: Yes, thank you. And it's a good follow-up to that last question. I have a clarifying question about the ad campaign that's being proposed during the executions and considering that the focus of this discussion is really looking at the perception of smokers to switchers, who will the ad campaign be marketed to? Will it be a broad public campaign or will it be to smokers only? And as a public health practitioner, I'm concerned about any initiation in young people and I'm not seeing that being carefully presented here.

DR. SHIFFMAN: So your question is how would the campaign be targeted so that it's, as much as possible, reaching the intended audience, and I think you're asking will it be targeted to teens. The short answer to that is no, but I'm going to ask Ms. Rachel Claxton, who is in charge of marketing for this product, to talk about the campaign and specifically, to talk about the controls that are in place to target the communication to smokers.

MS. CLAXTON: Good morning, my name is Rachel Claxton, I'm the Vice President of Consumer Marketing for Reynolds Brands.

The question relative to how do we ensure that we limit the use exposure to the media, print advertising as we're

speaking of here has two answers, one of which we will leverage some channels in which we will be directly carding or requiring enough personal information through the website, for instance, in order to third-party verify that the consumer is both a smoker and be 21 or older.

As it relates specifically to the print advertising that you've seen here this morning, we leverage print channels that only have more than 85% of their viewership at 18-plus or maybe an age of 23. So those different controls are in place against the limited media channels that we have applied to provide this data in.

DR. MERMELSTEIN: I have a list of Committee members who have questions to ask and so Dr. Ossip has been waiting for a long time, so I'm going to have hers, then we're going to take a break and come back and I've tracked the other people's questions which we will get to after our break.

DR. OSSIP: Thank you. I actually have a number of questions that track some of what's been asked, but let me ask one right now. If we look at, I think, maybe CC-124 from the modeling slides, this might be the best example.

And the question that I'm going to ask may apply to multiple of the paths, but I'll focus on the additional

initiation for now, because part of our consideration has to be how this will actually roll out at the population level and that will be in the context of a full marketing advertising campaign and I appreciate -- I'm sorry, I didn't catch your name.

DR. SHIFFMAN: Ms. Claxton.

DR. OSSIP: What you just presented in terms of the planned marketing. The experience of decades of tobacco products suggests that there may be perhaps unintended consequences of marketing products that even if the intention is to market them to just a specific population.

And so it seems to me, unless I missed something in the modeling, that it would be helpful to have some variants of that model that assume that that additional initiation is perhaps far greater than what you might anticipate in the context of a full marketing campaign and unintended ripple effects of that campaign and in this particular case, since additional initiation, if past history holds, may occur among youth.

The second part of the question is, are there particular concerns that -- of risk that would be unique to beginning at younger ages because either of some additional vulnerability of

youth compared to even young adults or other populations or simply, should they become long-term users, the length of use? Some of these are -- you know, these are "what ifs" but that, I believe, is the purpose of this kind of modeling to test alternate scenarios.

DR. SHIFFMAN: Yeah, absolutely. And I'm a splitter rather than a lumper, so I heard several questions in there and let me see if we can address each of them.

The first one, you mentioned that there have been studies, not with these ads, but with other ads specifically for snus among younger -- among teenagers and they showed no interest and, in fact, no increased interest if you make a health claim and as you saw in never tobacco users, we just don't see any expressed interest. But you're asking specifically about sensitivity analyses about that uptake, so I'll ask Dr. Curtin to address that.

DR. OSSIP: Or if I can clarify, it's the sensitivity analyses around that uptake or if there are additional assumptions that need to be folded in, that take into account if there are particular vulnerabilities to age of initiation, unique risks or risks that would be different depending on age of initiation.

DR. CURTIN: Okay, so let me point out that the model is driven by empirical estimates and we had empirical estimates from the likelihoods of use testing which showed us those very low numbers, probability for initiation among youth. Across all three advertising executions that was like 0.3%.

So there's some confidence that we see with what's been projected empirically and what we put into the model, because we're -- you know, if you were pressure testing that number, we used hypothetical probabilities of 50% for the gateway effect and we also did some sensitivity testing around if, in fact, that initiation number was higher. I showed earlier the multidimensional modeling we see, but in that multidimensional modeling you see that we can go, you know, fivefold of what was projected empirically, tenfold with fairly large numbers of gateway, and we just don't see that it requires a large number of switching to offset that. So I think that's what you're asking is have we tested and can it be higher? We have.

DR. OSSIP: Or if I can clarify it again, I want to make sure I understand this because I was looking very closely at the additional slide that you had shown, in the absence of gateway, so additional initiators who start with snus and stay with snus forever.

DR. CURTIN: Yes. So we had to make some simplifying assumptions in the model. We don't know exactly what the Camel Snus quit rates will be if, in fact, you tell someone it's a low risk product, which is what I think you're getting to. So in all the modeling, we didn't allow any Camel Snus quitting. In other words, we took that potential benefit off the table.

In the model, people can quit smoking like they would in the "what currently is" scenario, but once you become a Camel Snus user, you either can only transition to smoking or you remain a Camel Snus user for the duration of the follow-up. So there's no benefit for Camel Snus switching, it's a conservative approach, but we thought it was appropriate in the absence of data.

DR. SHIFFMAN: I think I can add a thought that may help, Dr. Ossip, which is that the model considers the duration of whether it's smoking or duration of snus as a big driver of the impact on health. So if you initiate earlier and, as Dr. Curtin indicated, the model doesn't even let you transition to abstinence, then it's going to estimate the risk is higher.

So it's taking into account the epidemiological data that shows the relationship between duration of use and health outcomes. And even with all of that considered, we see that

even with higher estimates of additional initiation that there is a substantial population benefit.

DR. OSSIP: Okay.

DR. MERMELSTEIN: Thank you.

I'm going to put a pause in the discussion for the moment. I know that we still have some people around the table whose questions we need to get to, but we will take a lunch break now. I'm going to ask everyone to do what's going to feel horribly unnatural, which is to not talk at all about the discussions that we've had all morning because they've been engaging and so I know that's going to be the challenge, but use all your wonderful self-regulatory skills and put them into play and we've got plenty of other topics to talk about, and we will reconvene at 1:15 so we can get through the rest of the day. Thank you.

(Whereupon, at 12:34 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

DR. SHIFFMAN: Our apologies. Dr. Giovino was very astute in noticing a discrepancy. The data were correct, the label of the axis was not. So this is dry weight, which is the way it's done in the U.S., in micrograms per gram, but the data are correct and they tell the same story, which is that Camel Snus is far lower than historical products.

And on Slide 2, these were correct to begin with, but this is now nanograms in wet weight for those of you keeping track, and it tells the same story as the Swedish historical products. So our apologies for that mislabeled slide.

DR. MERMELSTEIN: Thank you.

Okay, we're going to go back and just wrap up with a few Committee questions. Dr. Wackowski, you've been waiting patiently.

DR. WACKOWSKI: Hi. I had a question about the design choices for the advertisements. So we've been looking at three executions of a three-page ad and I appreciate that there were different executions of it, but the executions were very similar with just slight wording changes and I wondered if there were other draft executions, perhaps one-page versions,

two-page versions. I mean, there's a lot of information, so it brings up questions about potential, you know, literacy issues, are people going to actually read all of the information. You know, if it's in a magazine, are they just going to see the cover page that says no smoke equals less risk so I can think about switching, that kind of stuff?

DR. SHIFFMAN: So I think you've captured some of the -- which is that there is a lot of information, that we wanted to make sure we had balancing information as well as the modified risk information and because this is a product a lot of people aren't aware of, to also just make them aware of the product in general. But I'm going to ask Dr. Borgerding to speak to the process that we went through to design those ads.

DR. WACKOWSKI: And to follow up with that, with the testing of the understanding of it, whether there was any consideration for if people are just reading parts of it or -- yeah.

DR. BORGERDING: I'm Mike Borgerding, I'm a vice president at RAI Services Company. In terms of developing the advertising, we began with qualitative testing and just trying to understand information about how to communicate to smokers. It was done as a team activity, some of that team was

scientists and you may imagine that in the earliest rounds of testing we had ads that had much more science in them, more numbers, graphs, things that were communicating a more detailed version of the stories that you've seen today in terms of the available data.

What we found was that smokers aren't scientists, they don't want a scientific lecture, so to speak, they want simple, clear messages. And so we learned about what sorts of things would resonate with smokers in terms of their understanding or concerns and so on and that helped shape the advertising.

In terms of the advertising, as Dr. Ogden put forward, in the print advertising there are three panels. The first panel is a very, very simple panel and so it gives a very key message from the get-go, if you will, and then there's more information about the product and its manner of use and so on and then risk information. So it is chunked, as you heard before, it's the way that information seems to communicate well, and as Dr. Shiffman communicated and can address here in a moment, it's been well tested in terms of the understanding and perception of it.

DR. SHIFFMAN: And let me address your question about the testing. So the way it was presented and tested was that

people could read as much or as little of it as they wanted to. They were not told that there were going to be questions about their understanding of the ad afterward, so if they wished to, they could just look at the front panel and breeze through and again, this is parallel to having labels that are tested for over-the-counter products, which is watching. In that case, people are told that they're going be asked questions.

Here, they didn't know that there were going to be questions. They could read as little of it or as much of it as they wanted to. They could spend as little or as much time as they wanted to. So the idea was to test the ad and let people -- you know, if it was too much to read, we would see that in the results and in fact the results, we think, have been very positive.

DR. MERMELSTEIN: Thanks.

DR. WANKE: Thank you. So, given that we are asked to think about the reduction in risk, given how the products are actually used by consumers, I'm trying to get a handle on how the products are currently being used and the likelihood of complete switching since the reduction in risk requires that. And I'm also interested in finding out how those use patterns are reflected in the modeling, both current and projected use

patterns. So I have three sets of questions.

And so the first I wanted to ask is just a clarifying question from Dr. Ogden, from Slide -- it looks like CC-8, when you talked about that the flavors are adapted for the American palate using common smokeless tobacco and food ingredients.

And my understanding of just some of the feedback from anecdotal evidence from consumers and discussion boards is that Camel Snus, as a product, has a different flavor profile than, say, the Swedish snus or other products and that it's sweeter and that it doesn't have as strong of a tobacco flavor and also that given that it has a lower nicotine content, many users have reported -- and again, anecdotally.

And so I'm looking if you have some data in use patterns that might speak to this. And because of the lower nicotine content, many consumers don't find it as satisfying and I'm thinking of it in the context both of appeal and in the context of being able to support use -- complete switching as a tobacco product substitute and completely for cigarette smoking. And so I just wanted to confirm, is that anecdotal description of the comparison of the flavor and the appeal supported by the flavor of the product and the fact that it has more sweeteners added to it than, say, a Swedish snus product?

DR. SHIFFMAN: Okay, I'm trying to keep track and I think there were several questions in there. Let's see if we can address each of them. So, first, Dr. Ogden, with regard to the reformulation for American palate.

DR. OGDEN: Sure, I'll try to clarify some of the comments I made this morning. So one thing I would start off with is to realize that snus in Sweden is not a single thing. I mean, at last count, there are at least nine different manufacturers, there are hundreds of different styles.

Some of that information -- well, all of that information is proprietary to those manufacturers, but we do know from the literature and we do know from various websites the types of ingredients that are used there and these are very similar types of ingredients. Of course, we know for our own products what types of ingredients are used in traditional American smokeless products. So we're on high confidence that these are the same types of ingredients that are used in traditional American-style products. And of course, we know the taste signature is one that was actually tested and developed to appeal to U.S. smokers and that's an important characteristic.

I think your anecdotal observation, I have heard that as well, that typically snus in Sweden is a very different type of

taste experience. I've been to Sweden. Food in Sweden is often a different taste experience, as well, to Americans. So I think that is a difference, but they're the same types of ingredients, they're the same, obviously -- well, hopefully obviously, the same formulations, basic formulation and the same processing methods that are used in Sweden.

DR. WANKE: So would it be accurate to say that it does taste sweeter, that there are more sweeteners and it tastes sweeter?

DR. OGDEN: If I could, I would defer to Dr. Williams, who's head of our R&D and product development.

DR. WILLIAMS: Hey, good afternoon, I'm Aaron Williams. I was over smokeless product development when we developed snus. I'm currently the Senior Vice President of Research and Development at Reynolds.

We did finalize on three mint flavors and two non-mint flavors. We did test the Swedish-style snus in the U.S. with adult smokers and it did not test well with that flavor style and we ended up moving -- there's a salt/sweetness balance and they're a little higher in salt, a little less on sweet. Ours is a little opposite of that to meet with the U.S. palate.

DR. WANKE: And can you also speak to the nicotine

content, then, the comparison? I know that's something that we had --

DR. WILLIAMS: Sure.

DR. WANKE: Would it be accurate, then, just to say that it has a lower nicotine content?

DR. WILLIAMS: Well, there's a wide variety of nicotine levels in Sweden. They range from quite low to quite high. We buy the same tobaccos that are used for Swedish snus, so the nicotine in our tobacco content is the same. In some cases, you know, ours has been pretty consistent over time with the same tobaccos.

DR. WANKE: Okay, that's helpful. And thank you, I appreciate that, it helps me understand the context of maintenance of complete switching. And so then I wanted to ask about the epidemiology of --

DR. SHIFFMAN: Can we address the question before we move on?

DR. WANKE: Sure, absolutely.

DR. SHIFFMAN: So a couple of things. First, we're already in the market with not only more accurate information about not a lot of risk, but with a lot of inaccurate misperceptions, there's quite a bit of switching.

So the study by Shu-Hong Zhu, 40% of users of snus had switched from smoking and we have transition rates -- that's not been shown, but as I indicated, the data in our studies indicate that those transitions are often through dual use.

But there are also data from some of the clinical studies where satisfaction was measured and what you see -- and I'm going to ask Dr. Marano to speak to this -- is they asked people who used the product, their reported satisfaction with the product increases. Do you want to present that, Dr. Marano, please?

DR. MARANO: So we did look at appeal as people use the products and I'll show you some data from the study in which we recruited smokers to completely switch to Camel Snus, and may I see Slide 3, please?

So people were asked over -- sorry, this is actually data from a study where we asked smokers to reduce their smoking over 4 weeks and use snus in order to reduce their smoking and what you see here are basically the data that show, in Week 1, people were just smoking their cigarettes and this is their mean rating of their usual brand cigarettes in red.

And then in Week 2 they started using Camel Snus and we asked them to rate, on the same scale, how they felt about

Camel Snus, the acceptability of Camel Snus.

And the numbers across the top are numbers where we were asking them to reduce their smoking by that percentage over time, and what you can see is that the likeability of their usual brand cigarette actually decreased over time and then the appeal of snus actually increased over that same period of time. So you can see, at the end of that 4 weeks, that their ratings of both their usual brand cigarette and Camel Snus were very similar, almost identical.

DR. WANKE: So the percentage is what you've asked them to reduce their cigarette smoking intake or the --

DR. MARANO: Yes.

DR. WANKE: Okay.

DR. MARANO: That's correct.

DR. WANKE: So by Week 4 it would be 75% use of snus?

DR. MARANO: That was the goal.

DR. WANKE: Okay.

DR. MARANO: That was the target that we asked them to aim for.

DR. WANKE: Okay, that's helpful.

DR. MERMELSTEIN: Okay.

DR. WANKE: Thank you. And so then, what I didn't see is

an indication of what current use patterns are as far as do we know -- do you have data to say how many current cigarette smokers or how many cigarette smokers actually do uptake with Camel Snus and of those who do, who start using Camel Snus, how many switch completely and how many remain dual users?

DR. SHIFFMAN: We don't have it quite that way --

DR. WANKE: Okay.

DR. SHIFFMAN: -- but I can show you data, again, from the Zhu study to show you it's -- the other way. Of current snus users, if we can find that slide, and the Zhu study tabulated both dual use and they tabulated switching. Slide 3, please.

So what you can see, as I indicated earlier, there are several studies that converge on dual use being about half and of the snus use only, most of those, 30% of the total are complete switchers who used to smoke. If we look at actual transition probabilities, which I can show you --

DR. WANKE: Before you lose that slide, so this is snus but not specific to Camel Snus?

DR. SHIFFMAN: That's correct.

DR. WANKE: And would you say snus only are users that have probably never smoked; they took up snus and never smoked?

DR. SHIFFMAN: I should have explained this better. Yeah,

I think that's right. So 47% of users are using snus only and 6% out of that 46% or 47 are only using snus or only have -- just having smoked before, 40% switched from smoking to snus.

DR. WANKE: Right.

DR. SHIFFMAN: I hope that clarified.

DR. WANKE: And then 53% are dual users.

DR. SHIFFMAN: And by the way, I've gotten feedback that -- I'm speaking too quietly and people can't hear me, so let me know if that happens, I'll use my outside voice.

DR. MERMELSTEIN: Okay, we're going to -- did you have one more question, Kay?

DR. WANKE: Yeah, and then I wanted -- so I was curious, then, how those numbers translated into the use patterns that are reflected in the modeling. What I didn't see is the percentage -- the inputs that were presumed for the percentage of smokers who started using Camel Snus and of those, then, who were presumed to be the complete switchers versus the dual users. I wanted to know what the assumptions --

DR. SHIFFMAN: I'll ask --

DR. WANKE: -- in the model were.

DR. SHIFFMAN: -- Dr. Curtin to talk to that.

DR. CURTIN: Okay, to clarify, what you're looking for is

the probabilities that we used for switching? Is that the specific transition or were there other transitions you were interested in?

DR. WANKE: Of cigarette smokers, how many start using after they smoked and of those that start using, how many move on to be complete switchers versus maintain dual user.

DR. CURTIN: Okay, so we didn't have any empirical data on dual use, so in our modeling it's very straightforward what the simplifying assumption is. We take the empirical projections for continuing smokers, that is, smokers that were not likely to quit, they're interested in the product, that will make that complete switching, okay?

DR. WANKE: Okay.

DR. CURTIN: What we do is we do sensitivity testing. So as part of the model, I talked about these different harmful transitions which we used conservative estimates. So all our switching numbers in the modeling were immediately reduced by 50% for resumed smoking. So that's one way to take into account incomplete switching or dual use. And then we presented sensitivity testing which was down another three-quarters.

So we didn't have dual use in there directly, but we

addressed it with the way we modeled everything and the way we did the sensitivity testing, because what we wanted to do is pressure test this benefit we see, and we really think that the projection we got and the persistence in our projection with the sensitivity testing leads to an expectation of a population of benefit with Camel Snus.

DR. WANKE: So what would be the actual proportion that you're saying are completely switching? Of smokers, how many completely switch to snus as a class or is this snus, Camel Snus, specifically?

DR. CURTIN: It's Camel Snus, specifically.

DR. WANKE: Okay, specifically.

DR. CURTIN: And the way the model is set up is we look at these different 5-year age intervals and so the proportions in each 5-year age interval, starting with 13 to 17 and then 5 years, 5 years, the proportions across each population, those intervals start at about 0.6% switching and get less and less as you go down and get older.

So the youngest cohort, we'd have to see about 0.6% switching at each 5-year age interval. As they go through the follow-up, the next one is about 0.54 and eventually you get to the older ages where it's close to zero.

DR. WANKE: Okay. Thank you, that's very helpful.

DR. MERMELSTEIN: Just a couple more Committee questions and then --

DR. SHIFFMAN: I want to clarify something very important, which is as you saw from Dr. Curtin, the model separates smokers into those headed to quitting and not. So the figures he's giving you are for people not -- either not quitting or not headed to smoking, because there's a whole different calculus for people who are going to continue to smoke or headed to smoking.

DR. WANKE: Right, so the dual users are basically considered continued smokers?

DR. SHIFFMAN: Exactly.

DR. WANKE: Got it.

DR. SHIFFMAN: That only counts and --

DR. MERMELSTEIN: Great. Okay, we're going to move on to Dr. Duffy.

DR. SHIFFMAN: I don't think your mike is on.

DR. DUFFY: Okay. Sorry about that. My question has more to do with the labeling, and I was wondering about the benefits of switching backs that you spoke of. One of the benefits that was claimed was hassle-free tobacco, and I didn't see it in

today's presentation, but I saw it in some of the materials that were distributed. Another claim was swap the smoke for more freedom, and I wondered what the evidence or, at least, rationale was for those claims, and I was a little bit concerned about, you know, freedom in that, that's something that could be very appealing to youth.

DR. SHIFFMAN: So, indeed, that was ad Execution 1, and one of the transitions from Execution 1 to Execution 2 was the realization that that was not an optimal message, so that's why it's not in Executions 2 and 3.

I can ask someone to speak to hassle-free, but I don't think that was meant to be a claim, much less a health claim, but Dr. Borgerding can speak to that.

DR. BORGERDING: In terms of the development of the ads, there was qualitative testing of a number of different approaches to the advertising. The goal was to find advertising that communicated to smokers and to get smokers to switch completely to Camel Snus if they weren't going to quit using tobacco altogether.

And so there were various types of things that seemed to resonate with smokers through the qualitative testing and the key messages are about being free of cigarette smoking, not

having the things associated with cigarette smoking if you switch completely to Camel Snus.

As Dr. Shiffman indicated, along the way we looked at the advertising in Execution 1, looked at ways that we could do it differently, potentially improve it. That led to Executions 2 and 3. They're simpler in many ways in terms of the number of words present, in terms of the kinds of messaging and so on.

What we do find, though, in the testing that Dr. Shiffman shared with you, is that across the three ad executions, they test quite similarly in the various manners that they'd been evaluated. So while they are different words, while they are different in terms of the number of words even, they're quite similar.

But we evolved, for the reasons that I just indicated, to try and resonate with smokers, find ways to inform them that if they're not going to quit smoking and quit all tobacco, that Camel Snus would be a way that they could reduce risk for smoking-related disease.

DR. DUFFY: Thanks.

DR. MERMELSTEIN: Okay, Dr. Bierut.

DR. BIERUT: I have two questions. So the first one is the warning label that's on the print advertisement. Is that

going to rotate what the warning is?

DR. SHIFFMAN: Yes. The current law requires it has four warnings and they rotate and that is to be continued. The company is not asking for a change in labeling policy.

DR. BIERUT: And is one of the warnings -- just to remind, is one of the warnings about heart disease?

DR. SHIFFMAN: No. When we put out the warnings -- can I see Slide 1? So the warnings are that it can cause mouth cancer, can cause gum disease and tooth loss, that it's not a safe alternative, which is important, and that it's addictive. And these are not the company's choices, this is what the law mandates.

DR. BIERUT: Right. So I'm just going to make the comment that -- is that with the epidemiologic data that you've presented from both the United States and Sweden, there is this increased risk of heart disease with the snus product. And also looking at the results of the advertisement, for instance, Slide CC-87, about 20% of the people that are reporting that either they think that heart disease has no risk at all or they don't know. And so I'm just making that as a comment, that the warning labels don't seem to be connected and through no fault of --

DR. SHIFFMAN: Right.

DR. BIERUT: -- you guys, but it's just that it's not connected with what the epidemiologic data are saying.

DR. SHIFFMAN: Yeah. As you know, I don't speak for policy --

DR. BIERUT: Um-hum.

DR. SHIFFMAN: -- the policy, but I'm sure if people saw fit to add a heart disease warning, it would be added.

DR. BIERUT: Um-hum. So then my second question has to do with the -- like Slide CC-52. I don't recall hearing what the typical snus user was, you know, like how much, and the combustible cigarette user.

DR. SHIFFMAN: In the study, what was the typical use that's then reflected in these biomarkers, is that the question?

DR. BIERUT: Yes. So you're comparing --

DR. SHIFFMAN: Right.

DR. BIERUT: As I'm reading it, you're comparing a combustible smoker to then a snus user, and I don't have kind of a -- is it a 20-cigarette-a-day cigarette smoker and then the snus users using one packet a day?

DR. SHIFFMAN: Right.

DR. BIERUT: I'm just trying to get a perspective on what the use is.

DR. SHIFFMAN: I understand, I understand. So this study, if I am reading it correctly, this is the study where they weren't told what to do, they were just studying who came in the door. That said, Dr. Round can describe who was in the sample.

DR. ROUND: So in this study, we were recruiting people who self-reported either exclusive use of cigarettes or exclusive use of Camel Snus and I can show you the data in terms of their cigarettes per day for the exclusive smokers and the exclusive snus users. Is that what you're looking for? Yeah.

DR. BIERUT: Right, just to get a perspective of how heavily they're using in the different categories.

DR. ROUND: Sure, no problem. May I see Slide 2, please? Oops, sorry, not that one. Let's see a slide down. There it is, an exclusive -- I think we have the data. Sorry, that had the dual users and not the exclusive Camel Snus users. So the exclusive -- sorry?

DR. BIERUT: The dual use one was interesting too. It looked like they were using about two or three packs a day, two

or three pouches a day. I don't know what the phrase is, do you use pouches? Is that --

DR. ROUND: Pouches, yeah, that's it.

DR. BIERUT: So it looked like they were going from 18 to 15 and then two or three pouches. Okay.

DR. ROUND: And I can pull that up again if you'd like to see that, also, but --

DR. BIERUT: Yeah, my colleague --

DR. ROUND: Okay.

DR. BIERUT: My colleague would like to see that.

DR. ROUND: Okay, I'll start with the exclusive smokers --

DR. BIERUT: Okay.

DR. ROUND: -- then the exclusive snus users. The exclusive smokers smoked, as you saw, 18, about 18 cigarettes per day, that was their self-report. And in addition, the exclusive Camel Snus users used approximately two and a half cigarettes per day. Actually, sorry, I'm looking at the wrong data. No. Sorry, I know we have them. I don't want to misspeak here. Yeah, excellent. The exclusive Camel Snus users used about 3.8 pouches per day in that study. So that's 3.8 pouches and 18 cigarettes per day and I'll bring back up the dual use data. May I see Slide 3, please?

So here, there's the 18 cigarettes per day on the exclusive Camel -- exclusive cigarette smokers and then the dual users had slightly fewer numbers of cigarettes per day and about two pouches per day, in contrast to the exclusive Camel Snus users who were about four pouches a day.

DR. MERMELSTEIN: Okay.

DR. SHIFFMAN: We also have data from -- more of a population base than the survey, if you -- if that interests you.

DR. MERMELSTEIN: Okay, sure. Quick.

DR. SHIFFMAN: You ask a scientist if they're interested in seeing data.

DR. BIERUT: Right, good data and we want it.

DR. SHIFFMAN: Yeah. If I can see Slide 1, please? So this is from a large survey that Reynolds conducts and you can see the exclusive snus users, the dual users and smokers. So the dual users are using about five cigarettes per day less than smokers and they're using a lot less -- you know, this is again -- it's uses per day, but it basically translates to pouches, then the exclusive users. And there is a trend, then, in other population data that as people make the transition, cigarettes go down and snus use goes up. So I hope that helps.

DR. MERMELSTEIN: One last one from Dr. Wackowski and then --

DR. WACKOWSKI: I just had a quick clarifying question about the risk perception measures. So on CC-81 it was mentioned that both indirect and direct measures were used, so I just wanted to clarify.

When I read the materials and looked at the survey instrument, I was under the impression that the indirect measures were used to assess their beliefs about the risk of the product, the absolute risk, but that the direct comparison measure was used to ask what they think the ad was communicating regardless of whether it was their belief or not. So I just wanted to clarify if that's correct.

DR. SHIFFMAN: I'm looking to Dr. Polster, who ran the study. Yeah, he says it is.

DR. WACKOWSKI: Okay.

DR. SHIFFMAN: What I can tell you is that the two correspond quite well in our three executions, that is, that the people who say same level of risk have, you know, on the indirect measures, a timing increment and so on. So the two are very closely related.

DR. WACKOWSKI: That would explain why, on CC-86, there is

a large percent that say they think it's less risk than smoking.

DR. SHIFFMAN: Right.

DR. WACKOWSKI: What the ad will say, not necessarily their belief.

DR. SHIFFMAN: But we also see that in their beliefs. When we do the indirect measures, as I showed you in my presentation, that there's a reduction in risk and when we correlate the two, they correspond extremely regularly where what they say to this item and what they say to the two other affirmations is very close. As I suspect you will know, that distinction, and I see this in the work I do on OTC dry labels, it's very hard for people to make. They basically tell you what they think, no matter what you ask.

DR. WACKOWSKI: Thank you.

DR. MERMELSTEIN: Okay, just for Committee members on the phone, they get one last quick question from each of them and then we will be moving on. So we'll start with Dr. Kozlowski.

DR. KOZLOWSKI: Thank you. It's a question about the use of the mandated warning labels in the sample ads that you have. It appears that the same warning label is repeated on each page of the ad. Is there any regulatory reason why you couldn't use

a different official warning on each page of the ad?

DR. SHIFFMAN: Ms. Claxton can address that.

MS. CLAXTON: I'll jump at an opportunity to talk about warnings. So the ads have 20% in the advertising is required to carry the warning. There are four and they're intended to be regulated or rotated on a quarterly basis. So we wouldn't provide more than one warning at a given time in the marketplace and the intent of that is to ensure that we have an even amount of each warning that's provided over the course of the year.

DR. MERMELSTEIN: Great. From the phone, Sally Herndon.

MS. HERNDON: Hi. Two quick clarifying questions. Thanks for your presentation. One is when you defined smokers who were on the path to quitting, what's the time frame for that? I ask because, in my experience, most smokers are making attempts to quit at some point -- but that can be very variable in the course of a cycle.

The second question is related to Execution 2, the infographic. Say a little bit more about the statement, "Customize your enjoyment with up to 30 minutes of flavor per pouch." You talked a little bit earlier about sweetness and salt. Is that referring to those flavors or is it referring to

the nicotine hit that the user is getting? Or both.

DR. SHIFFMAN: Okay. Thank you for helping me by separating the questions. So the way the data were segmented and what I presented to you used the -- time frame for two reasons. One is, of course, smokers can't really project into the future all that far.

But secondly -- may seem like an odd interval, that matched exactly the time interval that the probability of use algorithm had used from that longitudinal study -- which were projecting who might use Camel Snus to match the period when people expected to quit. So there was a baseline -- time frame. In the modeling, of course, people have multiple opportunities when they may transition from smoking to quitting.

Your second question was about the flavors and 30 minutes and I'm looking around, Dr. Borgerding is prepared to answer that.

DR. BORGERDING: In terms of the infographic in the advertising, it's intended to give a smoker general information about snus. And in terms of the 30 minutes, it's trying to indicate that the flavor will last for, generally, that period of time.

In our experience, just empirically, not all users of Camel Snus would use the product for 30 minutes, some may use it longer, but we would expect the flavor would typically last that period of time, within that amount of time during use. It is not something that's intended to indicate anything other than about flavor.

DR. MERMELSTEIN: Thank you.

Dr. Giovino, you have the last question.

DR. GIOVINO: Okay, thank you. This is for Dr. Marano. Dr. Marano, in your presentation, towards the end you made a very sweeping comment about the data on switching for lung cancer and oral cancer and I believe you said were very convincing or were very strong. Given the lack of anything, any information on switching in terms of oral cancer in the 2007 Henley paper, I guess my first question is do you have the same level of confidence for oral cancer as you do for lung cancer, and if so, please share your reasons for that confidence with me and the Committee.

DR. SHIFFMAN: So specifically about switching and particularly, oral cancer, Dr. Marano.

DR. GIOVINO: Especially in comparison with lung cancer.

DR. SHIFFMAN: Right.

DR. MARANO: We do have the one slide that I -- the one study that I showed during the main presentation from Sweden. Can I see Slide 1, please?

So these are the data that we have for oral cancer among switchers from Sweden. Certainly, it's not as robust of a study as CPS-II and we do know that CPS-II is a much larger study and relative to the amount of data for lung cancer, it again is not as robust of a study. I believe we can be confident in the data. Can I see Slide 1, please?

Again, given what we know about oral cancer in general and the reductions in risk between smokeless tobacco and cigarette smoking, again, just seeing the consistency of the evidence, smokeless tobacco has much lower risk relative to cigarette smoking, which is the important thing, it's the relative risk and switching, in general, and the reductions that we see for the other three diseases based on the Henley paper.

DR. MERMELSTEIN: Thank you.

DR. GIOVINO: Okay. You know, the slide that's up there now is not about switching and we're being asked to consider a claim about switching and oral cancer. So is that the strength of your arguments? I mean biomarkers. Anything else in particular?

DR. SHIFFMAN: So I think the biomarkers are important and I'll ask Dr. Round to come up and talk about that and perhaps particularly for carcinogens, since you've asked about two different sites for cancer.

DR. ROUND: Overall, when we look at smokers who have switched completely to Camel Snus and we look at their differences and exposure to carcinogens, what we see is, overall, large reductions in exposure from smoking to switching to Camel Snus use.

DR. MERMELSTEIN: Okay, thank you.

DR. ROUND: I was just going to show the slide from the core one more time, our presentation, one more time, which is Slide 1, please. And, again, this was again smokers who were switched completely to Camel Snus.

The half-lives of these biomarkers are short enough that over this 5-day time period you would see the full extent of the biomarkers from switching to Camel Snus and here you see large significant reductions similar to abstinence. So their exposure to carcinogens from switching from smoking to Camel Snus is very low overall.

DR. GIOVINO: So I'd like to follow that up because I don't believe all of these biomarkers are relevant for oral

cancer; 4-aminobiphenyl is a bladder carcinogen. I think naphthalene, 2-amino naphthalene is the same. Which of these biomarkers would indicate risk for oral cancer?

DR. ROUND: Overall, we were looking at the totality of the carcinogens that were assessed and -- but if we wanted to look into specific biomarkers and specific constituents associated with specific diseases, I'll ask Dr. Heck to come up and comment on that.

DR. HECK: My name is Dan Heck. I'm a toxicologist and a principal scientist at Reynolds American Services.

As Dr. Stepanov mentioned, there may not be complete certainty about which carcinogens are effective in raising the oral cancer risk as opposed to lung cancer risk, but the combination of both cytotoxic irritating and genotoxic constituents, in combination, and in some ways we don't completely understand, elevates oral cancer risk quite significantly in smokers.

So I think that we may not have specificity with regard to oral cancer as much as we do, say, for lung cancer, but I think that whether it's one or the other and more likely the combination of all of these, including cytotoxic constituents, which tend to promote initiated tumors in both lung and oral

tissue, I think it's the combination of all of these as a net exposure reduced relative to smoking that provides the reduced risk.

DR. MERMELSTEIN: Thank you.

Dr. Tomar, did you have a quick question?

DR. TOMAR: Yes, thank you. So this actually goes back to the question about the dual use of snus, including Camel Snus, and then with the connection with cigarettes. You know, this product obviously is already on the market. Of your current consumers of Camel Snus, what percentage of those users are also currently using cigarettes as well?

DR. SHIFFMAN: So, again, there are three published population estimates and they all hover at around 50% of snus users are also smoking.

DR. MERMELSTEIN: Thank you.

DR. TOMAR: Thank you.

DR. MERMELSTEIN: Thank you. And that's all. Okay, I realize we went over with some of those questions, but --

DR. SHIFFMAN: We appreciate --

DR. MERMELSTEIN: -- thank you and I think a lot of it facilitated discussion later. We're going to move, then, to the FDA presentations.

DR. YOUNG: Good afternoon. My name is Dr. Mimy Young. I am a chemist in the Office of Science at the Center for Tobacco Products at FDA.

The first set of presentations will focus on the evidence related to the substantiation of the modified risk information. The product chemistry presentations will highlight evidence related to modified risk information around the reduction of harmful constituents in the six Camel Snus products compared to cigarettes. The toxicological, pharmacological, and epidemiological data will provide evidence that may be helpful in your assessments of the disease risk-related modified risk information.

Catherine Corey's presentation of the epidemiological evidence will outline the results from smokeless tobacco use studies related to the disease risk information submitted by the Applicant.

The second set of presentations will present on the Applicant's proposed advertisements and results from their consumer perception studies, as well as information about the likelihood of use of the proposed MRTPs, and specifically describe several observational studies that describe Camel Snus users, patterns of use, transition from cigarette smoking to

snus.

We will also describe findings from RJRT's clinical studies that relate to use of Camel Snus and findings from a self-reported likelihood of use study conducted by RJRT.

Here's a brief outline of the first presentation. I will first present the product chemistry of the six Camel Snus products and how they compare to cigarette products.

I will continue with the toxicological evidence summarized by my colleague, Dr. Kausar Riaz Ahmed, a toxicologist in the Office of Science at CTP and FDA.

I will then present the clinical evidence contributed by my colleagues, Susan Rudy, a health scientist; Dr. Theresa Carbonaro and Dr. Colin Cunningham, pharmacologists; and Christopher Ellison, a statistician. They're also in the Office of Science at CTP and FDA.

Catherine Corey will present the epidemiological evidence of this presentation.

In this section, I will discuss the Camel Snus product chemistry and the evidence submitted by the Applicant in the applications pertaining to the harmful and potentially harmful constituents, which I'll refer to as HPHCs, present in the six Camel Snus products and how it compares to mainstream cigarette

smoke and smokeless tobacco products.

The Applicant submitted MRTPAs for six Camel Snus products that are portioned snus smokeless tobacco products.

Snus is a type of smokeless tobacco product that is heat-treated tobacco contained in a pouch and held in the mouth during use. The Camel Snus products are described briefly in this slide. They are available in two pouch sizes and multiple flavors: a 600 mg pouch for Camel Snus Frost, Mint, and Mellow and a 1,000 mg pouch for Camel Snus Frost Large, Robust, and Winterchill.

The 600 mg products and the 1,000 mg products contain differences in product design such as pouch width, tobacco weight, pouch fleece weight and package weight.

All six Camel Snus products contain similar product design properties that include pH, moisture, tobacco particle size, pouch length, and formulation. The formulation of the Camel Snus products includes tobacco, salts, pH adjusters, sweeteners, flavorings, humectants, and pouch materials.

In comparison to cigarette products, the six Camel Snus products and cigarette tobacco products vary significantly in product design and formulation. The design of the products vary in components, product use, and route of administration.

For example, cigarettes contain tobacco within cigarette paper and glues that may incorporate a filter at the mouth end and deliver nicotine via inhalation. These components are not present in the six Camel Snus products; instead, the six Camel Snus products contain tobacco within pouch materials and delivers nicotine via oral route.

Although the six Camel Snus products and cigarettes contain tobacco, they contain different tobacco blends. American blend cigarettes contain tobacco leaf such as flue cured, burley, and oriental tobacco leaf as well as expanded tobacco and reconstituted tobacco. Differences in tobacco blends may result in differences in HPHCs.

Aside from the tobacco blend, both cigarettes and Camel Snus products contain ingredients added to the tobacco blend, such as flavors. Although the Camel snus products are composed of the same formulation, the six Camel Snus products differ in unique flavors that are different compared to cigarette products.

The six Camel Snus products and cigarette tobacco products also contain different quantities of ingredients, such as humectants and pH adjusters, that may potentially affect the levels of free-base nicotine, the form of nicotine that is

readily absorbed in human blood.

Scientific literature on tobacco filler and cigarette smoke is extensive, reporting that over 7,000 chemical compounds are present in mainstream cigarette smoke and approximately 4,000 chemical compounds are present in smokeless tobacco, identifying some of the harmful chemical constituents as carcinogenic.

The FDA published a list of 93 HPHCs in the *Federal Register* that I will refer to as the established HPHC list. These are chemicals or chemical compounds that are in tobacco products or in tobacco smoke that are or potentially are inhaled, ingested, or absorbed into the body, including as an aerosol, vapor, or any other emission and cause or have the potential to cause direct or indirect harm to users or nonusers of tobacco product with respect to five disease outcomes. That includes cancer, cardiovascular disease, respiratory effects, developmental or reproductive effects, and addiction.

From the FDA established HPHC list, 91 of the 93 HPHCs have been shown to be present in mainstream cigarette smoke, and 65 of the 93 HPHCs have been shown to be present in tobacco and smokeless tobacco.

From the FDA established HPHC list, 79 of the HPHCs are

classified as carcinogens, of which 77 carcinogens have been shown to be present in cigarette smoke and 51 carcinogens have been shown to be present in tobacco and smokeless tobacco.

FDA also published a draft guidance on reporting HPHCs in tobacco products and tobacco smoke under Section 904(a)(3) of the Food, Drug, and Cosmetic Act. This draft guidance is available for public comment and once finalized, it will represent the Agency's current thinking on the topics therein.

The draft guidance provides an abbreviated list for reporting HPHCs from several different chemical classes that have well-established analytical methods and are widely available. I will refer to this as the abbreviated HPHC list as shown in this slide.

The abbreviated HPHC list is categorized by product type, since different tobacco product types may contain different HPHCs. For example, the combustion involved in cigarette use contributes to a higher number of HPHCs, including carcinogens such as aromatic amines, volatile hydrocarbons, carbonyls, carbon monoxide, hydrogen cyanide, hydrazine, phenols, heterocyclic aromatic amines, and epoxides that may not be present in smokeless tobacco generally.

Some of the HPHCs reported in cigarette smoke are also

reported in smokeless tobacco product, as highlighted in red. The abbreviated HPHC list includes 18 HPHCs in cigarette smoke, of which 13 are considered carcinogens, and nine HPHCs in smokeless tobacco, of which eight are considered carcinogens.

The Applicant provided HPHC levels for the six Camel Snus products, cigarette products, and other smokeless tobacco products that includes moist snuff, dry snuff, and loose-leaf tobacco, in Section 7.1 of the MRTPA.

According to the Applicant, it provided the nine HPHCs in the abbreviated list for smokeless tobacco products. The Applicant also reported polycyclic aromatic hydrocarbons, or PAHs, listed in the established HPHC list for all tobacco products.

This table summarizes the HPHC levels in the six Camel Snus products and cigarette tobacco products from the RJRT analytical studies included in the MRTPAs. The Applicant states that they selected the cigarette and smokeless tobacco products based on market share, manufacturer, and elements of product design. Cigarettes from the study represents 51 to 60% of the U.S. cigarette market share in 2013 and 2014.

FDA compared the levels of the 15 HPHCs tested in the application on a per-unit-of-use basis, that is, per cigarette

for the cigarettes and per pouch for the portioned snus.

The second column lists the HPHC levels in the six Camel Snus products, the first number indicating the average HPHC levels for the 600 mg pouch products and the second number is the average levels in the 1,000 mg pouch products.

Mainstream cigarette smoke may be generated using two standard smoking regimens with different smoking intensity and puffing topography, shown in the third column of the table. The first number reports HPHC levels using a smoking regimen defined by the International Standards Organization, known as the ISO smoking regimen, and the second number reports the HPHC levels using a more intense smoking regimen known as the Health Canada Intense or CI smoking regimen.

The last column summarizes the average differences in the HPHC levels between all six Camel Snus products and in mainstream cigarette smoke. Highlighted in red are the constituents that are higher levels in the six Camel Snus products compared to mainstream cigarette smoke. That includes toxic metals, arsenic and cadmium, tobacco-specific nitrosamines or TSNAs, that includes NNN and NNK, and nicotine. These HPHCs are present in tobacco and have a lower transfer rate in mainstream cigarette smoke.

Also, the six Camel Snus products contain lower levels of carbonyl compounds such acetaldehyde, crotonaldehyde, and formaldehyde, and PAHs such as benzopyrene or B[a]P, and indenol(1,2,3-c,d)pyrene, compared to mainstream cigarette smoke.

Although it's not shown in the table, there are five PAHs in the Camel Snus products that are below the limit of quantification but are present in mainstream cigarette smoke at levels higher than the limit of quantification. These HPHCs are generally generated during the combustion of tobacco.

It must be noted that the six Camel Snus products and cigarette products are drastically different in product design and product use and does not necessarily reflect that users are getting the same amount or levels of HPHC exposure from each type of product, as shown in this table.

The actual exposure levels are influenced by factors such as user behavior, route of administration, rate of absorption, and metabolism. The exposure levels of the six Camel Snus products compared to mainstream cigarette smoke is further discussed in the toxicological, clinical, and epidemiological sections of this talk.

The scientific studies on Camel Snus products found levels

of HPHCs, specifically NNN, that is one of the major carcinogens in tobacco products, comparable to those reported in the MRTPAs, as shown in red. However, the levels reported have large variability.

Briefly, the main findings from these studies reported NNN levels in Camel Snus products ranging roughly 700 to 1800 ng/g from studies reported by Hatsukami, Stepanov, Borgerding, and Ammann. For further details, please see Section I-A of the FDA briefing document.

The Applicant also included analytical studies submitted in the MRTPAs for the six Camel Snus products and other smokeless tobacco products. The box plot illustrates the distribution of the NNN levels in moist snuff tobacco products, the six Camel Snus products, and Swedish snus tobacco products from the data submitted in the MRTPAs.

This shows that the median level, NNN levels, in the six Camel Snus products are comparable to moist snuff and higher compared to Swedish snus.

Also, the box plot illustrates this region of the NNN levels in mainstream cigarette smoke using the two standard smoking regimens which show that the six Camel Snus products and other smokeless tobacco products contain higher levels of

NNN compared to mainstream cigarette smoke.

Differences in the NNN levels in the six Camel Snus products and moist snuff may be due to key differences in the manufacturing process. The six Camel Snus products undergo a heat treatment process generally used in the manufacturing of Swedish snus tobacco products, but different from the fermentation process used in the manufacturing of moist snuff tobacco products.

The Applicant states that the six Camel Snus products are manufactured using the same processes and procedures as Swedish snus that minimize the potential for microbial activity and has greater impact on lower quantities of HPHCs when compared to other forms of smokeless tobacco.

In Sweden, the manufacturing of snus is regulated by a Swedish National Food Agency directive that sets limits of certain constituents such as TSNAs and B[a]P.

In addition, GOTHIATEK is a voluntary quality standard for snus. In comparison to the levels set by the GOTHIATEK standard, the sum of the levels of NNN and NNK in the six Camel Snus products are higher compared to the GOTHIATEK standard limit of 0.95 µg/g.

In summary, the six Camel Snus products contain two

different pouch sizes with differences and similarities in product design and formulation, but the main differences between the six Camel Snus products is the unique flavor ingredients.

In comparison to cigarette products, the six Camel Snus products and cigarette products are different in product design, tobacco blends, and ingredients other than tobacco.

The differences in product design also affect the HPHCs present in the six Camel Snus products and mainstream cigarette smoke.

Although thousands of chemical constituents have been identified in smokeless tobacco and cigarette smoke, the MRTPAs reported chemical constituents in the six Camel Snus products limited to those in the abbreviated HPHC list, but the same number of HPHCs in Camel Snus products that are also present in mainstream cigarette smoke.

Among the HPHCs measured, the six Camel Snus products contained lower levels of carbonyls, acetaldehyde, crotonaldehyde, and formaldehyde and PAHs, but contained higher levels of arsenic, cadmium, NNK, NNN, and nicotine compared to mainstream cigarette smoke.

Although the Camel Snus products are manufactured

similarly to Swedish snus, the HPHC levels in Camel Snus exceed the levels set by the GOTHIATEK standard, with median NNN levels in Camel Snus comparable to that in moist snuff.

NNN has been known to cause oral cancer in smokeless tobacco users. Therefore, Swedish snus may not be appropriate for evaluating certain disease risks, for example, oral cancer, in the six Camel Snus products. Instead, the scientific literature on U.S. smokeless tobacco products may be appropriate for the evaluation of some disease risk in the six Camel Snus products that will be discussed in the epidemiological section.

I will now present data related to the toxicological effects of Camel Snus products being evaluated in the MRTPAs.

As previously mentioned, the MRTPAs include analytical measurements for HPHCs measured in the six Camel Snus products evaluated in the MRTPAs and cigarette smoke.

As indicated in the previous slides, the HPHCs detected in cigarette smoke were also detected in the six Camel Snus products. Of the HPHCs measured, acetaldehyde, formaldehyde, crotonaldehyde, and B[a]P, representative PAH, are lower in the six Camel Snus products as compared to cigarette smoke. However, five of the HPHCs from the RJRT analytical studies

included in the MRTPAs, specifically, arsenic, cadmium, NNK, NNN, and nicotine, are higher in the six Camel Snus products than cigarette smoke.

Adverse human health effects associated with each of these HPHCs are provided in this slide. For example, nicotine is addictive as well as a reproductive and developmental toxicant. Arsenic, cadmium, NNK, and NNN are carcinogens. NNN is considered the primary driver of oral cancer in users of smokeless tobacco products.

It is important to note that differences in portal-of-entry effects, differences in toxicant absorption and distribution through the body and differences in metabolism can affect the toxicity of HPHCs introduced through different routes of exposure.

The application contains study reports for in vitro assays intended to evaluate the genotoxic potential of the six Camel Snus products with comparator cigarettes and other smokeless tobacco products.

A preliminary evaluation of the results from the in vitro genotoxicity studies indicate that extracts from the six Camel Snus products and other smokeless tobacco products, as well as the extracts from total particulate matter collected from

comparator cigarette smoke, all tested positive for genotoxicity in vitro.

The Applicant submitted data from in vivo studies conducted in rodents exposed to Camel Snus native tobacco blend and the aqueous extract of the Camel Snus native tobacco blend. The studies did not use the Camel Snus products in their final form and did not include comparator products. These limitations make it difficult to use these studies to make conclusions on the health effects of the six Camel Snus products, as well as how these products compare to cigarette smoke and other smokeless tobacco products.

I will now briefly discuss the clinical studies RJRT submitted and present data on biomarkers of exposure.

The Applicant provided information about eight clinical studies sponsored by RJRT. Study documents can be found in Section 7.4 of the MRTPAs, Section I-C and III-B in the FDA briefing document, and in a summary table provided in Appendix B.

The studies were conducted from 2007 to 2012 and include two Camel Snus single exposure, nicotine pharmacokinetic studies, five repeated exposure Camel Snus studies ranging in length from 5 days confined to 52 weeks ambulatory use with

various comparators, and one study with natural product adopters who reported product use for at least 6 months.

The Camel Snus products assessed in these studies are Camel Snus 600 mg pouches in Frost and Mellow flavors, limited data with the 1,000 mg pouch in Winterchill flavor, and 400 mg pouches in Frost, Spice, and Original flavors, which are not a subject of the MRTPAs. Not all six Camel Snus products were studied.

For the next few slides, the specific product used in each study is denoted in the footnotes.

Over 150 biomarkers were assessed. Biomarkers of exposure were assessed in three studies: Study 0702, which was a 24-week study switching from cigarette smoking; Study 0901 was a 5-day confined use study switching from cigarette smoking; and Study 0904 was a cross-sectional study of natural product adopters. Biomarkers of potential harm were assessed in two studies: 0702 and 0904.

RJRT chose biomarkers they believe to represent inflammation, oxidative stress, and other physiologic processes. However, due to the issues in design and statistical analysis, as discussed later, and the number of biomarkers showing no difference between the studied Camel Snus

product users, cigarette smokers and non-tobacco users, biomarkers of potential harm will not be discussed in detail, but more information can be found in Section I-C in the FDA briefing document.

We will now discuss RJRT's conclusion of the biomarkers of exposure data. Twenty-four weeks of 400 mg Camel Snus use reduced 18 of 21 biomarkers compared to levels from baseline usual brand cigarette smoking.

In a 5-day confined use study with exclusive use of 600 mg Camel Snus Frost and Mellow products and/or use of cigarettes and Camel Snus products lowered 26 and 23 of 28 biomarkers compared to baseline usual brand smoking, respectively.

Exclusive Camel Snus users had lower concentrations of 22 biomarkers compared to dual users.

Among natural product adopters, exclusive smokers and/or users had higher levels of 18 and 16 of 26 biomarkers compared to exclusive Camel Snus users of Frost, Mellow, and Winterchill products of which data were pooled. Biomarkers of exposure were generally not different from -- not different between exclusive smokers and/or users.

Importantly, exclusive or dual use of Camel Snus products did not lower TSNAs. Smokers, Camel Snus users, and dual users

had lower TSNAs compared to users of moist snuff comparators.

Only two biomarkers of exposure, the TSNAs NNN and NNAL, were assessed in three independent research studies. As discussed further in the FDA briefing document, TSNAs were generally not different after repeated exposure to Camel Snus use, either 5 days confined use or 4-week ambulatory use compared to usual brand smoking at baseline.

Of note, only one study used products that were subject of the MRTPAs. The other two used 400 mg products.

Hence, Camel Snus products may lower exposure to some biomarkers but may not lower TSNA-specific exposure.

Next, I'll highlight some of the important factors of these studies that could limit some of the Applicant's interpretations and conclusions.

First, data were provided for varieties of 400 mg pouch products; however, justification was not provided to adequately bridge the data to the 600 or 1,000 mg products in the application.

Second, there are design and analysis problems associated with several studies. Although RJRT reported statistically significant decreases of several biomarkers of exposure, it's unclear whether those differences are clinically meaningful.

In addition, data from more than one Camel Snus product were combined for assessments, not aligned for individual product comparisons.

Furthermore, data were analyzed by assignment which did not always reflect actual use or inclusion criteria, since dual use was common.

Also, in Study 0904, which studied a large number of both biomarkers of exposure and potential harm, participants' self-selection into product type may have biased the results.

In addition, hundreds of comparisons were made without adjustments for multiplicity and may have resulted in numerous statistical false positives and false negatives.

And now Catherine Corey will come present the epidemiological evidence.

MS. COREY: Hello, my name is Catherine Corey. I'm an epidemiologist at CTP. I will be discussing long-term epidemiological evidence on smokeless tobacco use, cigarette smoking, and risk for selected tobacco-related diseases that relate to the proposed MRTPAs.

During this presentation I will give an overview of FDA's review of the epidemiological evidence; describe studies and findings characterizing risks of lung cancer, oral cancer,

heart disease, and COPD according to tobacco use status; present evidence pertaining to additional diseases and tobacco use behaviors; and provide a summary for the Committee.

This presentation provides epidemiological evidence on disease risks associated with smokeless tobacco use compared to non- or never tobacco use from U.S. based studies. Additional data from Swedish studies are reported in the FDA briefing document.

Analyses of HPHC yields reported earlier in this presentation indicate that certain harmful constituents, including TSNA NNN, a potent carcinogen, in the six Camel Snus products exceeds levels in Swedish snus sold in the U.S. and are comparable to levels of other U.S. moist snuff comparator products.

While constituent and exposure levels can vary across smokeless tobacco products, 92 of the relative risks associated with U.S. smokeless tobacco use and with Swedish snus use are generally more similar to each other as compared to the relative risks for cigarette smoking.

Epi studies typically provide disease risk information pertaining to smokeless tobacco products generally, including products referred to in the literature as chewing tobacco,

snuff, dip, or spit. The Applicant did not present, nor are we aware of, long-term epidemiological studies specifically pertaining to the six Camel Snus products that are the subject of the MRTPAs.

Among studies providing multiple risk estimates, we focus on the estimates for exclusive current or ever smokeless tobacco users, those who never smoked cigarettes, and are to isolate the effects of smokeless tobacco use on disease risk.

The relative risks for exclusive smokeless tobacco users are based primarily on three U.S. cohorts that assess fatal disease events.

Finally, we focus on estimates produced from published meta-analyses since the summary relative risks are generally considered more robust than estimates from single studies.

RJR did not submit, nor is FDA aware of, evidence directly comparing the disease risks for continuing smokers to the risks for former smokers who switched to exclusively using any smokeless tobacco product. That comparison would've provided additional relevant evidence to evaluate the Applicant's modified risk information that focuses on complete switching from cigarettes to the six Camel Snus products.

For the proposed modified risk claims relating to lung

cancer, oral cancer, respiratory disease and heart disease, published relative risks were evaluated for the following tobacco user groups:

- Exclusive smokeless tobacco users compared to non- or never tobacco users, derived primarily from published meta-analyses;
- Exclusive former smokers who switched to exclusive smokeless tobacco use at the time of or after quitting smoking, referred to as switchers, compared to never tobacco users and compared to former smokers who quit all tobacco use based on information from the Cancer Prevention Study, or CPS-II; and
- Exclusive current cigarette smokers compared to never smokers from CPS-II, published in the 2014 U.S. Surgeon General's report.

This table, presented as Appendix C of the FDA briefing document, summarizes study characteristics of the three U.S. cohorts that are primary sources of evidence for disease risk associated with exclusive smokeless tobacco products, generally.

From left to right are the first National Health and Nutrition Examination Survey, or NHANES-I, epidemiologic

follow-up study. The Cancer Prevention Study, or CPS-I and last, CPS-II, were sponsored by the American Cancer Society. We know that these cohorts were conducted at varying time points from the 1960s through 2000 -- in terms of follow-up time and sample sizes of exclusive smokeless tobacco users, typically ascertain tobacco status only at baseline and assess mortality risks for many tobacco-related diseases.

This table presented as Table 9 of the FDA briefing document summarizes characteristics of the only study we are aware of that examined mortality risks among exclusive former smokers who switched to exclusive smokeless tobacco use at the time of or after quitting smoking, referred to as switchers. The study was conducted by Henley and colleagues and were allowed in the CPS-II cohort.

This analysis consisted of male participants of CPS-II who were followed for 20 years from 1982 to 2002. Mortality risks for switchers were directly compared to the risks for two groups, former exclusive smokers who quit all tobacco products and never tobacco users, and analyzed using models that address it for a range of demographic, prior cigarette smoking, and other risk factors.

With that overview, we'll review the evidence for disease

risk for lung cancer, oral cancer, heart disease and respiratory disease, specifically COPD, according to tobacco use status.

This table, provided Table 8 of the FDA briefing document, presents summary relative risks from meta-analyses by Boffetta et al., Lee and Hamling, Lee, and Boffetta and Straif. They examined associations between smokeless tobacco use and disease risk in U.S. based studies. Meta-analysis estimates from Swedish snus studies are also summarized in Table 8 of the FDA briefing document.

From Lee and Hamling we report three results described by them as overall data, smoking adjusted, and never smoker because those authors stratified their results based on the extent of adjustment for smoking and other factors in the original studies, whereas the other meta-analyses generally produce single summary relative risk estimates according to geographic area.

The sample size, or *n* in parentheses, refers to the number of original study estimates that were included to produce the summary relative risks in the meta-analyses.

Starting with the results for lung cancer, the meta-analyses from both Boffetta et al. and Lee and Hamling report

elevated but not significant associations for lung cancer just according to exclusive ever smokeless tobacco users compared to never tobacco users.

For oral cancer, both Boffetta et al. and Lee and Hamling reported elevated risks of oral cancer among ever U.S. smokeless tobacco users compared to nonusers. The results from Lee and Hamling indicate that the relative risk for oral cancer are sensitive to the adjustment or restriction by smoking status.

For heart disease, Boffetta and Straif reported an elevated risk of heart disease just among exclusive ever U.S. smokeless tobacco users compared to never tobacco users, whereas Lee reported an elevated but not significant association.

This table, presented as Table 10 of the FDA briefing document, provides the hazard ratios among exclusive former smokers who switched to exclusive smokeless tobacco use at the time of or after quitting smoking, referred to as switchers, compared to former smokers who quit all tobacco and compared to never tobacco users.

Looking at the second column, switchers had higher risks of death compared to former smokers who had quit all tobacco,

for lung cancer, oral cancer, heart disease, stroke, and all causes in analyses that adjusted for previous cigarette smoking behaviors, sociodemographics, and other behavioral and dietary risk factors.

Looking at the third column, switchers had higher risks of death compared to never tobacco users, for lung cancer, heart disease, COPD and stroke in adjusted analyses. Results were not reported for fatal oral cancer and for all-cause mortality among switchers compared to never tobacco users.

This figure, presented in Section 6115 of the Applicant's MRTPAs and is Figure 2 of the FDA briefing document, summarizes the relative risks by disease for three tobacco use groups: exclusive current cigarette smokers compared to never smokers, the bar in yellow, based on CPS-II results reported in the Surgeon General's report; former smokers who switched to exclusive smokeless tobacco use compared to never tobacco users, the bar in purple, from CPS-II reported in the prior slide; and exclusive smokeless tobacco users compared to non- and never tobacco users, the bar in blue, based on meta-analysis results that were presented two slides ago.

For lung cancer and for COPD, the relative risks are substantially elevated among exclusive cigarette smokers

compared to never smokers, while the risks are smaller but still elevated among switchers compared to never tobacco users, and while the risks are elevated but not statistically significant among exclusive smokeless tobacco users compared to never tobacco users.

For oral cancer, relative risks are substantially elevated among exclusive smokers compared to never smokers, while the risks are smaller but elevated among exclusive smokeless tobacco users compared to never users. Information from CPS-II was not provided on the risks of fatal oral cancer among switchers compared to never tobacco users.

For heart disease, relative risks are elevated among exclusive smokers compared to never smokers. Relative risks are smaller but still elevated for switchers and for exclusive smokeless tobacco users' benefits compared to never tobacco users.

We'll now transition to reviewing the evidence pertaining to other disease risks and disease risks associated with certain tobacco use behaviors.

The proposed advertising executions include certain modified risk statements that refer to less risk associated with the use of the six Camel Snus products without identifying

specific diseases. There are diseases and health outcomes for exclusive use of smokeless tobacco products in general, does not pose lower risk than smoking or the magnitudes and the differences in risks may be unclear.

For adverse pregnancy outcomes, a review by Inamdar, examining nine studies conducted in geographic regions that include the U.S., Sweden, Asia, and South Africa found associations between smokeless tobacco use and stillbirth, preterm birth, low birth rate, and small for gestational age. The authors note that the study quality varied and findings may have been limited by methodological issues inherent in the studies and included bias and confounding.

A review by Lee in 2014 reported on four studies from the Swedish medical register which found increased risk among exclusive snus users during pregnancy compared to non-tobacco use for conditions including stillbirth, preterm birth, and neonatal apnea. For these conditions, the relative risks among exclusive snus users compared to never users were similar in size to the relative risks among smokers compared to never users.

The Applicant did not submit evidence related to possible associations between smokeless tobacco use, generally, and the

risk of Type 2 diabetes.

A recent U.S. cohort study reported that current smokeless tobacco users had higher measures of insulin resistance including fasting plasma glucose levels and insulin levels at baseline compared to never users after adjusting for covariates.

A positive association was reported between former smokeless tobacco use and Type 2 diabetes during 10 years of follow-up when adjusting for demographic characteristics; however, no associations were found in fully adjusted models.

A pooled meta-analysis of five cohort studies from Sweden found snus use was associated with an increased risk of Type 2 diabetes compared to never tobacco users. At the highest levels of snus use, the relative risks were similar in magnitude to those for cigarette smokers.

The proposed advertising executions also include certain modified risk statements that do not explicitly describe the consumer behavior that is intended to lower disease risk. For example, no smoke equals less risk. Of concern is the potential for persistent dual use of cigarettes and the six Camel Snus products that are the subject of the MRTPAs.

Among the Applicant's cited U.S. studies that examined

lung cancer, oral cancer, and heart disease, the relative risks for dual use of cigarettes and smokeless tobacco were generally comparable in magnitude to the relative risks for exclusive smokers.

A review by Lee in 2014 assessed risk of circulatory diseases, cancers, pregnancy related conditions, chronic inflammatory diseases, in four groups: users of Swedish snus only, only cigarettes, dual users, and never tobacco users.

While Lee reported that the relative risks among dual users were not higher than the risks among smokers, the data also suggested that across different disease endpoints the relative risks for dual use were generally comparable in magnitude to the relative risks for exclusive smokers, believes the potential that smokers may replace some cigarettes with use of the six Camel Snus products without fully quitting smoking.

Epidemiological studies evaluating disease risk associated with reductions in smoking intensity have had mixed findings. For example, some studies have observed significant reductions in lung cancer risk associated with at least a 50% reduction in cigarettes per day; however, other studies did not observe a change in disease or mortality risk with reduction in smoking intensity.

The lack of consistent findings in these studies may be due in part to variations in the definitions of smoking reduction, differences in the dose response relationship by different disease endpoints, and the potential for smoking compensation among self-reported reducers.

There are several considerations with respect to the epidemiological evidence presented. We assessed disease risk associated with U.S. smokeless tobacco products generally. The Applicant did not present, nor are we aware of, epidemiological studies specifically pertaining to the six Camel Snus products that are the subject of the MRTPAs.

We noted the relative risks for exclusive smokeless tobacco users are based primarily in three cohorts that assessed failed disease events: NHANES, CPS-I, and CPS-II. While we presented U.S. epi evidence, we know that the magnitude of the relative risks associated with U.S. smokeless tobacco use and with Swedish snus use are, in general, more comparable to each other than they are as compared to the relative risks for cigarette smoking.

The U.S. cohorts typically ascertained tobacco use only at baseline and had extended follow-up time and were to accrue sufficient numbers of disease events. These factors could lead

to misclassifications of tobacco exposure if, for example, some users quit smokeless tobacco use after the baseline survey which would weaken associations between smokeless tobacco use and disease risk.

Additionally, the cited studies were conducted over several decades in practice, including healthcare treatment, tobacco use patterns, and constituent exposures may have changed over time.

Finally, the CPS-II study by Hamling is the only one, to our knowledge, that examined disease risk from former smokers who began using exclusive smokeless tobacco use at the time of or after quitting exclusive cigarette smoking and compared those risks to the risks of former smokers and never tobacco users. Hamling did not compare the risks among switchers to the risks of continuing smokers. That comparison would've provided additional relevant evidence to evaluate the Applicant's modified risk information that focuses on complete switching from cigarettes to the six Camel Snus products.

In summary, the relative risks for lung cancer and respiratory diseases, specifically COPD, are substantially elevated in exclusive cigarette smokers compared to never smokers. The relative risk magnitudes are smaller but still

elevated among switchers from cigarettes to smokeless tobacco products compared to never tobacco users. There is no conclusive evidence linking exclusive smokeless tobacco product use with either of these conditions.

For oral cancer, relative risks were substantially elevated among exclusive smokers compared with never smokers. Information is not available on the risks of fatal oral cancer among switchers compared to never tobacco users, although the risks of oral cancer among switchers were elevated compared to the risks of former smokers. Compared to smokers, the relative risks are smaller in size but still elevated among exclusive smokeless tobacco product users in the U.S. compared to never users.

For heart disease, relative risks are elevated among exclusive smokers compared to never smokers. Compared to the risks for smokers, the relative risks were somewhat smaller in size but still elevated for switchers and exclusive smokeless tobacco users where the common referent is never tobacco users.

Continuing the summary, the adverse pregnancy outcomes are among conditions for which the relative risks for exclusive smokeless tobacco users are generally similar to the relative risks among exclusive smokers.

While for Type 2 diabetes differences in the magnitude of the relative risks for exclusive smokeless tobacco use and exclusive smokers are unclear.

Relative risks for dual use of smokeless tobacco products and cigarettes are generally comparable to the risks of exclusive smoking.

With that, we'll conclude the presentation on the evidence related to the substantiation of the modified risk information.

Next, Erin O'Brien will present on the evidence that relates to Camel Snus use and consumer perceptions.

DR. O'BRIEN: Hello, my name is Dr. Erin O'Brien, and I'm a social scientist at FDA, and I'll be presenting evidence summarized by my colleagues and me that relates to Camel Snus use and consumer perceptions. And my colleagues that helped prepare this presentation are Dr. Coleman and Dr. Cunningham.

This is the FDA disclaimer.

This is an overview of what I'm going to be talking about today:

- Information on Camel Snus users based on observational studies.
- Information on Camel Snus users based on clinical studies.

- Research on general perceptions of smokeless tobacco, including snus.
- RJRT's proposed advertising material that contain modified risk information.
- What we know about modified risk information and consumer perceptions of Camel Snus based on RJRT's studies, and
- Information on the effect of modified risk information on the likelihood of Camel Snus use based on RJRT's studies.

I wanted to point out two abbreviations on these slides. ST refers to smokeless tobacco and MR refers to modified risk.

We will start by examining current use of Camel Snus without the proposed modified risk information. You can find this in Section III of the FDA backgrounder.

The Applicant's primary source for survey data on characteristics and patterns of Camel Snus use among adults was the National Tobacco Behavior Monitor, or NTBM. NTBM is a nationally representative cross-sectional survey administered monthly online to adults who are of legal age to purchase tobacco. Approximately 2,000 surveys are completed each month, and analyses of the NTBM data and the MRTPAs use data collected

from January of 2013 through March of 2016.

To compare estimates to the NTBM on demographic characteristics and patterns of use, the Applicant provided additional evidence in the applications from RJRT's consumer Brand Tracker and publicly available data from the Population Assessment of Tobacco and Health Study, or PATH Study.

FDA analysis of the NTBM data show that 0.5% of adults report past 30-day use of Camel Snus. This estimate is consistent with an independent analysis published by Chang and colleagues of the PATH Study, which found that 0.4% of adults at Wave 1 reported current use of pouched snus products.

Descriptive analyses from the NTBM suggests that demographic characteristics of adult current Camel Snus users are generally consistent with current users of other smokeless tobacco products. Specifically, both current users of Camel Snus and current users of other smokeless tobacco are predominantly between the ages of 25 and 49, male, identified as Caucasian, and generally report greater versus lesser educational attainment.

These findings from the NTBM are also consistent with descriptive analyses of RJRT's Brand Tracker data as well as other published estimates from the PATH Study.

In terms of patterns of Camel Snus use, observational studies provided by the Applicant, as well as from the peer-reviewed literature, suggests that the majority of Camel Snus users are dual or poly users of other tobacco products including other smokeless tobacco and cigarettes.

Lastly, while the Applicant focuses on adult use patterns in its actual use studies and in the applications, published estimates of pouched snus use, and smokeless tobacco more generally, suggests that current use among youth in the U.S. is low.

The Applicant did not provide evidence from population-level studies to directly assess the likelihood that U.S. cigarette smokers would switch either to smokeless tobacco products or Camel Snus more specifically.

However, there are a few studies that provide some insight on likelihood of switching, including clinical studies submitted by the Applicant, as well as evidence from the broader peer-reviewed literature.

First, the Applicant conducted a randomized controlled trial that compared the efficacy of Camel Snus and nicotine replacement therapy for smoking cessation. Results indicated that there were no statistically significant differences in

smoking cessation rates between study groups. And this was the case even among those who received one-time information on the relative risks of smokeless tobacco and cigarette use. Moreover, at the end of the study, smoking quit rates were generally low for all cessation endpoints.

Similarly, a published randomized controlled trial by Hatsukami and colleagues examined the role of Camel Snus versus nicotine replacement therapy in smoking cessation. Investigators found no statistically significant difference in switching from cigarettes to either Camel Snus or nicotine replacement therapy at Week 6 or Week 12 of the trial.

Lastly, in a systematic review of observational studies of cigarettes and smokeless tobacco transitions, investigators found that switching from exclusive cigarette smoking to exclusive smokeless tobacco use among adults was low, with transitions from exclusive smoking to dual use of cigarettes and smokeless tobacco being slightly more common.

As noted previously, RJRT did not provide evidence from population-level data to directly estimate the likelihood of switching from cigarettes to Camel Snus in a real-world setting. Instead, the Applicant used data from the NTBM to compare frequency of cigarette smoking, that is, number of days

in the past week among past 30-day exclusive cigarette smokers to dual users of Camel Snus and cigarettes.

Findings suggest, first, that dual users of cigarettes and Camel Snus, or those in the first column, were less likely to report near daily or daily use of cigarettes compared to exclusive cigarette smokers.

Second, dual users were more likely to report smoking on 0 to 1 days of the past week or on 2 to 5 days of the past week compared to exclusive smokers.

Lastly, in a weighted linear regression analysis looking at trends of cigarette use frequency from 2013 to 2016, NTBM found that the frequency of cigarette use declined over time among dual users of cigarettes and Camel Snus, whereas frequency of cigarette use among exclusive smokers remained unchanged.

To summarize, findings from real-world observational studies, including studies submitted by the Applicant as well as evidence from the broader peer-reviewed literature, suggests that the prevalence of pouch snus use generally, and Camel Snus use specifically, among U.S. adults is low at less than 1%.

Characteristics of Camel Snus users in the U.S. appear to be generally consistent with users of other smokeless tobacco

products with respect to age, sex, race, and educational attainment.

Moreover, concurrent use of Camel Snus with other smokeless tobacco products and cigarettes was common across studies.

Across multiple lines of evidence, research conducted with cigarette smokers under real-world conditions suggests that few would completely switch to Camel Snus or other smokeless tobacco products.

Okay, now I will very briefly review information related to switching from cigarettes to Camel Snus from the clinical studies. And you can find this in Section III of the FDA backgrounder.

RJRT provided reports and data from clinical studies which provide insight into use behaviors of tested Camel Snus products that are the subject of these applications.

As described previously, eight clinical studies were submitted. Two of these studies were nicotine pharmacokinetic or PK studies. Five involved repeated exposures, which varied from 5 days up to 52 weeks. And one study was conducted on natural product adopters who primarily used Camel Snus Frost and Mellow in 600 mg pouches.

The majority of clinical studies submitted by RJRT examined the effects of Camel Snus Frost or Mellow in 600 mg pouches. As someone otherwise noted, data for the submitted studies were obtained using one or both of these products with the data pooled.

One study, however, examined Camel Snus Frost, Spice, and Original in 400 mg pouches, which we should note are not products included in the current applications.

These clinical studies examined biomarkers of exposure and potential harm and these results were presented earlier. They also examined nicotine exposure, pharmacokinetics, tobacco product use behaviors, and subjective effects such as measures of liking, dependence, and withdrawal.

The Applicant's clinical studies show that the tested Camel Snus products that are the subject of these applications appear to have lower abuse liability than cigarettes. We know from the literature that the complete substitution of a product with relatively low abuse liability for a product with relatively high abuse liability is unlikely.

In the Applicant's studies, the nicotine exposure pharmacokinetic profile for the Camel Snus products is overall less than those found for cigarettes.

When subjective measures such as liking were compared between the two, tested Camel Snus products produced similar or lesser subjective effects than cigarettes. This includes potentially lower abuse liability of the tested -- this indicates potentially lower abuse liability of the tested Camel Snus products.

In the Applicant's clinical studies, dual use of the Camel Snus products and cigarettes was common.

Additional evidence of tested Camel Snus products, not serving as a complete substitute for cigarettes, can be found by examining study compliance and completion rates, which were typically low.

In one submitted study, participants were tasked with reducing number of cigarettes per day, or CPD, by 75% while also using Camel Snus Frost or Yellow [sic] in 600 mg pouches. Participants only reduced CPD by an average of 59% by the end of the study. This may indicate that it is difficult to make the transition between cigarettes and the tested Camel Snus products.

Another clinical study used 400 mg Camel Snus pouches, which are not the subject of these applications. In this study, the Camel Snus group was the least likely to complete

the study and be compliant when compared to heated tobacco product and combustible cigarette groups. Compliance was defined as participants using Camel Snus as at least 75% of the total amount of their tobacco use. In fact, only 55% of the per-protocol subgroup was classified as compliant, meaning that even under instructions participants did not exclusively use Camel Snus.

Now I'm going to shift gears away from behavior. Next, I will summarize usage on risk perceptions of smokeless tobacco, including snus. You can find this information in Section II of the FDA backgrounder.

I wanted to start with an overview of how people perceive the risks of smokeless tobacco, in general, and snus, specifically.

A number of studies in the peer-reviewed literature have looked at this. Here are the results of two studies of perceptions of smokeless tobacco and snus without modified risk information.

The first, if you look at the upper left, most U.S. adults believe that snus is both harmful and addictive. Further, if you look right below that, when we just look at cigarette smokers we see a similar finding, most believe that snus is

harmful and addictive.

The graph on the right illustrates a few interesting points. First, if we look at a sample of young adults, we can see that average ratings for both snus and smokeless tobacco are very similar.

Second, we can see that for all groups, average ratings are pretty high. For all groups, average ratings are between the top two response categories.

Third, we can see that tobacco nonusers, the first group to the far left, perceived the products to be higher risk than other tobacco users, including cigarette only, cigarette and other tobacco product users, and other tobacco product users only. And this is what we'd expect as it's a pattern of results that we see in the literature in studies of perceptions of different tobacco products.

In sum, most U.S. adults perceive smokeless tobacco and snus as harmful and addictive.

This slide illustrates some of the literature on relative harm perceptions, that is, how harmful people believe that smokeless tobacco and snus are compared to cigarettes.

Here we can see that in three studies of U.S. representative samples, a minority of adults and youth believe

that snus and smokeless tobacco are less harmful than cigarettes. Across studies, this is about 7 to 12%. You can also see that across studies results are largely consistent. You can also see that about half of U.S. adults and youth believe that smokeless tobacco and snus are equally harmful to cigarettes, and 22 to 38% believe that smokeless tobacco and snus are more harmful. So more people believe that smokeless tobacco and snus are more harmful than cigarettes than believe they are less harmful than cigarettes.

Another finding to note on the bottom right and consistent with the last slide, in terms of relative harm perceptions, current tobacco users are a little bit more likely to rate smokeless tobacco and snus as less harmful than cigarettes compared to former and never users.

Now that we have a general understanding of how people perceive the risks of snus and how they perceive snus compared to cigarettes without modified risk claims, I'm going to talk about what RJRT is proposing.

RJRT is proposing three different versions of advertising, called executions, to market six Camel Snus products with modified risk information. You can find these in Section 4 of the MRTPAs and Section II of the FDA backgrounder.

Each execution contains three main types of information: general information about the product, modified risk information, and what RJRT referred to as balancing information that says, for example, the product is addictive.

These executions are similar to one another, with several differences. Execution 1 was developed first. Execution 2 was developed to simplify Execution 1, including reducing the reading level. Execution 3 is identical to Execution 2 with two health effects removed, heart disease and oral cancer.

RJRT proposes to advertise Camel Snus in a variety of print and online channels and submitted sample advertising for each execution for print ads, handouts, direct mail, a website, and promotional emails.

In general, the print ads included the largest amount of information, and ad materials for other channels contained a subset of that information.

And I wanted to clearly note that all of the submitted advertising materials contain modified risk information. However, none of the submitted product labels contain modified risk information. Further, RJRT is not proposing to make any changes to the currently required warnings for smokeless tobacco products.

I think we are having a mouse -- is there an extra mouse or I can keep going and make the best of it, otherwise, but --

(Off microphone response.)

DR. O'BRIEN: Okay.

DR. MERMELSTEIN: Why don't we take a brief break?

DR. O'BRIEN: Yes. It's changing to the next one, so --

DR. MERMELSTEIN: Do a break now. So let's take a 10-minute break and we'll come back and wrap up.

(Off the record at 3:09 p.m.)

(On the record at 3:20 p.m.)

DR. MERMELSTEIN: Okay, Dr. O'Brien, are you ready to continue?

DR. O'BRIEN: Yeah.

DR. MERMELSTEIN: Okay, let's go.

DR. O'BRIEN: Okay, I'm going to do this slide again because that's where things got weird last time. So starting back with an overview of RJRT's proposed advertising, RJRT proposed three different versions of advertising, called executions, to market six Camel Snus products with modified risk information. And you can find these in Section 4 of the MRTPAs and Section II of the FDA backgrounder.

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I wanted to clearly note that all of the submitted advertising contains modified risk information. However, none of the submitted product labels contain modified risk information. Further, RJRT is not proposing to make any changes to the currently required warnings for smokeless tobacco products.

This is an overview of the modified risk information

across all three advertising executions that FDA is evaluating. Because this is a lot of information to process, I'm going to walk you through a specific example to help explain what consumers would see.

This is the Execution 2 print advertisement and I selected this as the example because it has the most in common with the other executions. It's a simplified version of Execution 1 and it differs from Execution 3 only in the health effects included.

As you can see, this is a three-page ad and much of the second page offers general information about the product and how to use it. This includes information about the five different flavors and two different pouch sizes available.

Both the first and third page contain modified risk statements. For example, the first page says, "No Smoke, Less Risk." The third page includes several statements including "Smokers who switch completely from cigarettes to Camel Snus can greatly reduce their risk of lung cancer, oral cancer, respiratory disease, and heart disease" and "Switching to Camel Snus means less of the harmful chemicals found in cigarette smoke."

The last thing that I wanted to point out is what RJRT

referred to as balancing information. For example, the second page says, "Camel Snus contains nicotine and is addictive." And the third page has a section with further information titled "No tobacco product is safe." This includes information about the product being addictive, who should not use the product, and that smokers concerned about their health should quit and talk to a healthcare provider.

Here's the advertising adapted to another channel. This is a handout intended to be distributed in person to age-verified tobacco consumers age 21 or older. You can see that it shares many of the same elements as the print ad, but contains only a subset of the print ad's information. There's less general product information, though it contains several modified risk statements. It also contains the same "No tobacco product is safe" section as the three-page print ad.

Now I'll review RJRT's research on understanding risk perceptions of Camel Snus after being exposed to ads with modified risk information. And you can find more information on this in Section 7.5 of the MRTPAs and Section II of the FDA backgrounder.

RJRT conducted three studies to assess consumer understanding and perception of Camel Snus after viewing these

ads. Here's an overview of the key features of these studies.

Each study had the same objective, to assess whether consumers understood key communication messages and the health risk perceptions of using Camel Snus. One study was conducted on each print ad execution. Each study was identical in the methods. Each study had the same design; it was non-experimental and post-test only, so there were no different conditions and everybody saw the same ad. And they were conducted using an online survey.

The sample was recruited from the Research Now online panel, and participants had to be at least legal age to purchase tobacco in their state of residence. It included current, former, and never tobacco users. Sample sizes ranged from about 5,000 to 8,000 participants and all participants were shown the same ad with modified risk information. There was no control group.

And, again, these ads featured five different flavors of Camel Snus and indicated that two different pouch sizes were available.

Because participants were asked about Camel Snus in general, rather than any specific Camel Snus product, we refer to Camel Snus products in general in this portion of the

presentation.

Participants were shown the ad with one "understanding" question per page of the survey. After this, they enter risk perception questions without being shown the ad. Analyses were limited to descriptive statistics, there were no comparisons of any kind made using inferential statistics, and data was weighted to be nationally representative.

In this presentation I'm not going to go over results for every single item, but instead I'm going to review results of key outcomes. The first key outcome was risk perception ratings of Camel Snus, smokeless tobacco other than Camel Snus, and cigarettes. These were made on a one-to-seven scale where one was no risk and seven was substantial risk. Each of these products was rated for risk of lung cancer, oral cancer, respiratory disease, heart disease, generally poor health, and addictiveness.

The second key outcome was understanding. We will focus on three items:

- Is quitting the best choice for a smoker who is concerned about the health risks from smoking?
- Should adults who do not use or who have quit using tobacco products start using Camel Snus?

- And a question that gets at how smokers need to use the product to get a health benefit, whether they need to stop smoking completely and use Camel Snus instead, or whether they can continue to smoke and use Camel Snus as well.

I also wanted to note that there was a third answer option in the study of the first ad execution that was not present in the studies of the second and third ad executions. This option was reduce smoking by half and use Camel Snus in addition.

Here are the risk perception results for all participants. This graph shows average risk perception ratings of Camel Snus for the six different health conditions. You can see that, overall, mean risk perception ratings are in the moderate to high range, all above the midpoint of the scale, which is four. They're lowest for lung cancer and respiratory disease and highest for oral cancer and addiction.

You can also see that across executions risk perception ratings are similar. One exception worth noting is that risk perceptions for oral cancer are higher in Execution 3 compared to the other executions. In Execution 3, oral cancer was not included in the modified risk information.

Finally, this is not shown in the graph but consistent

with the literature, results indicate that current tobacco users had lower risk perceptions compared to former and never users.

These graphs show comparisons of risk perceptions of Camel Snus, smokeless tobacco other than Camel Snus, and cigarettes. The four graphs on the left assess risk perceptions of diseases specifically mentioned in the modified risk information and in the ad Executions 1 and 2: lung cancer, oral cancer, respiratory disease, and heart disease. The modified risk information in Execution 3 was limited to lung cancer and respiratory disease.

Across health conditions we see the same trend. Risk perceptions are highest for cigarettes, lower for smokeless tobacco other than Camel Snus, and slightly lower for Camel Snus. The differences between products are most pronounced for lung cancer and respiratory disease and less pronounced for oral cancer and addiction.

This slide reviews responses to three key "understanding" outcomes. We can see that most participants responded correctly to the first two questions, that quitting tobacco is the best choice for smokers concerned about the health risks from smoking, and that tobacco nonusers should not start to use

Camel Snus.

You can also see that most people responded correctly that, according to the ad, smokers need to switch completely, that is, stop smoking and start using Camel Snus, to receive a health benefit from using Camel Snus.

We also note that Execution 1 included an additional response option: reduce smoking by half and use Camel Snus. About 10% of the sample selected this option, indicating that some people think that they get a health benefit from using Camel Snus by replacing some smoking with using Camel Snus. And, again, this answer option was not included in the studies of Execution 2 and 3.

RJRT also provided results separately for several key subgroups, but they did not provide statistical tests that assess whether these subgroups differed from the overall sample.

These subgroups included:

- Tobacco experimenters;
- Potential quitters;
- People with limited health literacy;
- White men;
- Racial or ethnic minorities; and

- Young adults.

There was no discernible pattern of how these subgroups differed from the overall sample. No particular group was consistently higher or lower than the overall sample across health effects based on comparing 95% confidence intervals.

For example, people with limited health literacy rated lung cancer and respiratory disease risk as higher than the overall sample, but they rated risk of oral cancer, generally poor health, and addiction as lower than the overall sample.

So our main takeaway is that there were no clear patterns of subgroup differences in Camel Snus risk perceptions.

RJRT also looked at subgroup differences for the "understanding" questions. In comparing subgroups, we note a few trends worth mentioning. Two subgroups seemed a little bit more likely to get answers wrong compared to the overall sample: people with limited health literacy and tobacco experimenters.

About 10% fewer people with limited health literacy answered the first question correctly about quitting being the best choice for smokers concerned about their health.

About 10% fewer people with limited health literacy and tobacco experimenters answered the second question correctly

about tobacco nonusers starting to use Camel Snus.

For Question 3, on what smokers need to do to receive a health benefit from using Camel Snus, we looked at differences in two different response options. If we look at the Execution 1 study, which included the response option of reduce smoking by half and use Camel Snus, we can see that experimenters were almost twice as likely to pick this compared to the overall sample. And it looks like people with limited health literacy and potential quitters were also more likely to select this option. While about three-quarters of the overall sample answered this question correctly, only 53 to 65% of people with limited health literacy answered this question correctly.

I wanted to mention two main limitations of these studies. First, the Applicant did not provide a robust assessment of perceptions of risk reduction from dual use. As this is the predominant use pattern, we think it's important to understand whether people who partially switch think that they are getting the risk reduction described in the modified risk information.

Second, these studies were not experiments that assessed the effect of modified risk information on perceptions and understanding. Because the studies did not include control groups, we cannot determine to what extent results reflect the

effects of the modified risk information versus participants' preexisting perceptions. However, five peer-reviewed studies did experimentally assess the effect of modified risk and relative risk information on perceptions of smokeless tobacco and snus products. These studies found that exposure to this information decreased risk perceptions of smokeless tobacco and snus relative to cigarettes.

So this provides some evidence suggesting that results from the current studies do reflect a causal effect of exposure to the modified risk information.

So, in summary, peer-reviewed studies find that in the absence of modified risk information, most people perceive snus as harmful and addictive. And most people perceive snus as equally or more harmful compared to cigarettes.

RJRT has proposed to use three advertising executions to market six Camel Snus products as MRTPs and they aren't proposing to include modified risk information in product labels. And they also did not propose altering the current smokeless tobacco warning labels.

RJRT's studies found that most people thought, after seeing the three-page ad with modified risk information, that Camel Snus was moderate to high risk for diseases, lower risk

than cigarettes, and slightly lower risk than other smokeless tobacco products.

One limitation was a lack of assessment of perceptions of risk from dual use, which is important because it's the predominant use pattern.

The other limitation is that the effect of the modified risk information on perceptions and understanding was not assessed in these studies. The studies were not experiments with a control group.

However, published studies that did experimentally assess the effect of modified risk information on perceptions of smokeless tobacco and snus find that it reduces perceived risk of smokeless tobacco and snus compared to cigarettes.

The last thing I'm going to talk about is how the proposed modified risk information in RJRT's three-page ad affects the likelihood that different smoker groups will purchase Camel Snus for trial, that is, the self-reported likelihood that current, former, and never smokers will purchase it for trial. You can find more information on this in Section 7.5 of the MRTPAs and Section III of the FDA backgrounder.

So this is an overview of studies RJRT sponsored and called likelihood of use studies. These studies assess the

effect of the proposed modified risk information on likelihood of purchasing Camel Snus for trial.

Three studies were conducted, one on each of the three executions of the three-page print ad. Each study included about 11 to 14,000 participants. The studies were identical to one another in every way except for the specific print ad shown to participants. Participants were recruited from the Research Now online panel and were adults who were of legal age to purchase tobacco in their state, up to 75 years old. They were sampled using quotas based on tobacco use and included current, former, and never tobacco users.

In each of the three studies, participants were randomly assigned to see either the full three-page print ad with modified risk and balancing information or the exact same ad with modified risk and balancing information removed. This was the control. The ads featured five different flavors of Camel Snus and indicated two different pouch sizes were available.

Participants then responded to the question "Assuming this product were available today, how likely would you be to purchase Camel Snus in order to try it?" Response options ranged from one, definitely would not purchase it to try, to 10, definitely would purchase it to try. Because participants

were asked about Camel Snus in general rather than any specific Camel Snus product, we refer to Camel Snus products in general in this portion of the presentation.

Analyses figured the data to be nationally representative and they involved comparing ratings between the modified risk and the control groups. They also converted these likelihood of use ratings to predicted percent likelihood that they would purchase the product for trial using an algorithm developed in previous studies.

RJRT transformed self-report likelihood of purchase ratings, the main outcome, into predicted purchase probabilities using an algorithm they developed in a longitudinal study. This study involved conducting an online survey where participants rated likelihood of purchase of any variety, for example, Red or Gold, of a new sub-brand of Marlboro cigarettes, Marlboro Special Blend.

They made this rating on the same 1 to 10 response scale that you saw in the previous slide. They collected this data 2 weeks prior to marketing this new sub-brand. Then, 9 months after this new sub-brand was launched, they surveyed the same participants to assess whether they had actually purchased any variety of this new sub-brand. They used this data to convert

the self-reported ratings to predicted purchase probabilities, taking into account age and tobacco use status.

The table on the right displays the predicted purchase probabilities for various age -- for various age groups and user statuses that reported a four on the likelihood of purchase question.

RJRT also conducted two studies using the same methodology to validate the algorithm. Both studies were of specific new varieties of a then-existing sub-brand rather than for a new sub-brand, overall. One study was of new varieties of Marlboro Special Blend, Blue and Black, and the other was for a new size in an existing specific flavor of Camel Snus, Camel Snus Frost Large.

And results indicated that the algorithm's overall predicted purchase rates were about one to two percentage points higher than actual purchase rates.

So although this conversion of self-reported ratings into predicted purchase probability is useful, it's important to keep this limitation in mind when interpreting results.

So here are the results for the overall sample combining all smoking statuses. You see the mean likelihood of purchase ratings on the lowest part of the 10-point scale and range from

1.7 to 2.0. You can also see that in Executions 2 and 3, mean ratings were significantly higher in the modified risk group compared to the control group. These differences were small, 0.1 on a 10-point scale.

When these ratings were transformed into predicted purchase probability, taking into account age group and tobacco user group, an estimated 1.3 to 1.7% were likely to purchase it for trial following the single exposure to an advertisement.

Predicted purchase probabilities were significantly higher in the modified risk condition than the control condition for Executions 2 and 3 by a small amount, 0.2%.

However, these results are generally qualified by an interaction between experimental group and smoker status. To illustrate this interaction, I'm going to present results separately by smoking status.

So here are the results for current smokers. We see that mean likelihood of purchase ratings are on the lower part of the 10-point scale and range from 2.8 to 3.8. We can also see that across executions, mean ratings were significantly higher in the modified risk group compared to the control group.

When these ratings were transformed to predicted purchase probability, taking into account age group and tobacco user

group, an estimated 5.8 to 8.2% were likely to purchase it for trial.

Predicted purchase probabilities were low, but significantly higher in the modified risk condition than the control condition for Executions 2 and 3, but not for Execution 1.

Here are the results for former smokers. We see that mean likelihood of purchase ratings are between the two lowest points of the scale, one and two. We can also see that across executions, mean ratings were not affected by the presence of modified risk information; they did not differ by condition.

When these ratings were transformed to predicted purchase probability, an estimated 1.9 to 2.2% were likely to purchase it for trial. These predicted purchase probabilities also did not differ by condition.

I'm having bad luck today. There we go, okay. So, lastly, here are the results for never smokers. We can see that mean likelihood of purchase ratings are between the two lowest points of the scale, one and two. We can also see that across executions, mean ratings were not affected by the presence of the modified risk information; they did not differ by condition.

When these ratings were transformed to predicted purchase probability, an estimated 0.4 to 0.5% were likely to purchase it for trial. And these predicted probabilities also did not differ by condition.

RJRT's findings are generally consistent with similar peer-reviewed studies that tested the effects of modified risk and relative risk information on likelihood of use. Although these studies differ from RJRT's and the stimuli in the modified and relative risk information tested, it's informative to see how RJRT study results compare with relevant literature.

Although there are few exceptions, these studies generally found that modified risk and relative risk information slightly increased likelihood of using the product for current smokers but did not affect likelihood of using product for former and never smokers.

Overall, you can see that RJRT's results are largely in line with the literature and they also found that modified risk information caused a small increase in likelihood of using the product for current smokers but did not affect likelihood of use for former and never smokers.

So, to summarize, RJRT studies that involved a one-time exposure to the three-page print ads found that the presence of

the proposed modified risk information on Camel Snus ads increases the proportion of smokers that are likely to purchase Camel Snus for trial by about 1%, does not affect likelihood of purchase for trial for former and never smokers.

And these studies also found that when shown an advertisement with the proposed modified risk information, about 5.8 to 8.2% of smokers are likely to purchase the product for trial and about 2% of former smokers and 0.4% of never smokers are likely to purchase it for trial. However, these purchase-for-trial results could be an overestimation.

RJRT's findings are generally consistent with similar peer-reviewed studies that tested the effects of modified and relative risk information on likelihood of use, that is, in both RJRT's and most published studies, modified and relative risk information generally slightly increased likelihood of use among smokers, but not among nonsmokers.

Now I'd like to provide a quick overall summary of FDA's presentation. I'll start by summarizing evidence related to substantiation of the modified risk information based on chemistry and toxicological evidence.

The scientific studies report 4,000 chemical compounds are shown to be present in smokeless tobacco and over 7,000

chemical compounds are shown to be present in mainstream cigarette smoke.

However, all HPHCs RJRT tested were present in both cigarette smoke and the six Camel Snus products.

The differences in routes of exposure, portal-of-entry effects, toxicant absorption, distribution throughout the body, and metabolism can affect the toxicity of the HPHCs.

The in vitro studies tested positive for genotoxicity from extracts of the six Camel Snus products, other smokeless tobacco products, and extracts from total particulate matter collected from cigarette smoke.

Clinical evidence shows that during a 5-day confined study, exclusive and all users of the proposed Camel Snus MRTPs using the 600 mg Frost and Mellow had lower levels of several biomarkers of exposure compared to baseline cigarette smoking.

Furthermore, in a population of natural adopters, exclusive but not dual use of the proposed MRTPs had lower levels of several biomarkers of exposure.

However, exclusive or dual use of Camel Snus did not lower TSNAs. In addition, smokers as well as Camel Snus exclusive and dual users had lower TSNAs than other moist snuff users.

This slide summarizes the epidemiological evidence related

to the substantiation of the modified risk information.

The relative risks for lung cancer, COPD, oral cancer, and heart disease are elevated in exclusive cigarette smokers compared to never smokers.

Though smaller in magnitude compared to smokers, the relative risks for oral cancer and heart disease are elevated in exclusive U.S. smokeless tobacco users compared to nonusers. And there's a lack of a consistent association between exclusive U.S. smokeless tobacco use and lung cancer or COPD.

The relative risks for lung cancer, COPD, and heart disease for former smokers who have switched completely to exclusive smokeless tobacco use compared to never users are smaller than the relative risks for exclusive smokers, and these relative risks are generally larger than the relative risks for exclusive smokeless tobacco users.

The relative risks for oral cancer among switchers compared to never tobacco users are not available.

Relative risks for adverse pregnancy outcomes are generally similar for exclusive smokeless tobacco users and for smokers, while for Type 2 diabetes, the size of any differences in the relative risks for smokeless tobacco users and smokers is unclear.

Relative risks for dual users of any smokeless tobacco and cigarettes are generally comparable to the relative risks of exclusive smokers.

This is a summary of the evidence regarding Camel Snus use patterns that was provided in the material submitted in the MRTPs. MRTPAs, excuse me.

The evidence showed that prevalence of pouch snus or Camel Snus use among U.S. adults is pretty low, and that dual or poly use of Camel Snus with other tobacco products, such as other smokeless tobacco and cigarettes, was common.

There was also evidence that observational and clinical studies suggest that few smokers would switch completely to Camel Snus or other smokeless tobacco. And dual use of Camel Snus and cigarettes was quite common.

Lastly, clinical studies showed that Camel Snus appears to have lower abuse liability than cigarettes under the conditions that were tested.

Lastly, I will summarize information on consumer perceptions and likelihood of purchase of Camel Snus.

Peer-reviewed studies find that in the absence of modified risk information, most people perceive snus as harmful and addictive, and most people perceive snus as equally or more

harmful compared to cigarettes.

RJRT studies found that most people thought, after seeing a three-page ad with modified risk information, that Camel Snus was moderate to high risk for diseases, lower risk than cigarettes, and slightly lower risk for other smokeless tobacco.

Other RJRT studies that involved a one-time exposure to the three-page ad found that the presence of modified risk information on Camel Snus ads increases the proportion of smokers that are likely to purchase Camel Snus for trial by about 1% and did not affect likelihood of purchase for trial for former and never smokers.

And that concludes FDA's presentation. We have several slides with our references and I believe we have time for clarifying questions.

DR. MERMELSTEIN: Dr. Ossip.

DR. OSSIP: Thank you. And thank you for the presentations. I have actually two questions, the first is for Dr. Corey and the second is for Drs. Corey and O'Brien.

The first is, I think -- Dr. Corey, I think is from your presentation. Is there anything that you can share with us about the meaningfulness of the similarities and differences

between the smokeless tobacco users in NHANES and CPS-I and II that will help us in looking at these in light of the six products that we're considering?

MS. COREY: In terms of the study characteristics for the participants in NHANES, CPS-I, CPS-II, the populations there consisted generally of adult tobacco users, so I believe the CPS studies included adults 35 and over. The NHANES had included adults ages 45 and older. The CPS studies included predominantly males, which is generally the subpopulation in the U.S. that is most predominant with respect to smokeless tobacco use and the NHANES study included a small sample of women as well as men.

With respect to sort of the frequency of use and use characteristics, is that also something that you're interesting in understanding or can you provide a little bit more specifics?

DR. OSSIP: Yeah, and about the smokeless tobacco products themselves.

MS. COREY: The products themselves. Yeah, there have been some shifts over time with respect to what types of products are most popular in the market. Currently, moist snuff products, my understanding is that those are the

predominant share of the overall market and that's grown over time. So previously, snuff products tended to -- I'm sorry, chewing, chewing tobacco tends to be more popular. So there have been shifts and changes in the popularity of different products, smokeless products, in the U.S. over time.

DR. OSSIP: Thank you. And for both of you, maybe. Since we're considering the population impact and the history of tobacco products is that there is uptake among youth when new products are launched, whether intended or unintended.

Are there any data that you can point to for us that specifically focus on children and youth? We have some young adult data that we've seen starting at age 18, but among younger populations what the potential impact may be, be it from the biomarkers, be it from the toxicity or even be it from the perceptions.

DR. O'BRIEN: I'm going to let Dr. Coleman start this one.

DR. COLEMAN: Hi, I'm Dr. Blair Coleman, epidemiologist at CTP. So since the products have been on the market, we have some evidence to suggest that, you know, youth use of the products is low. We have data from the National Youth Tobacco Survey from 2014, that was the last survey year to look at snus in particular, and since then it's been a composite of

different smokeless tobacco products and the use of smokeless tobacco among youth has been lower and has been shown to decrease over time.

DR. OSSIP: So we've seen or we're -- I think most or at least many of us are probably aware of the prevalence data, but I think that's something different because that's prevalence data before there's a concerted marketing campaign around --

DR. COLEMAN: That's right.

DR. OSSIP: -- the modified use tobacco product. So, you know, particularly, I guess, questions about are there unique exposure, toxicity, health impacts for youth and then is there anything informative about their perception of these products? Again, it would be in the absence of a concerted marketing campaign, but that might inform our assessment of the broader population impact.

DR. O'BRIEN: We have one study that published PATH data on perceptions of snus among youth and we found that, at least in terms of relative harm perceptions, they're pretty much the same as adults, between youth and adults.

Unfortunately, we don't really have much either from the Applicant or in the peer-reviewed literature on the effect of modified risk information and whether that differs on -- the

effect of modified risk information is different for youth versus adults.

DR. OSSIP: Thank you. And anything on any of the biomarkers or unique health risks or concerns for -- are they a particularly vulnerable population? Is their vulnerability different from risk, a health risk standpoint relative to adults, for these products?

DR. KITTNER: I'm afraid we don't have that information.

DR. OSSIP: Thank you.

DR. KING: Yes, thanks. So I have three questions, one for each presenter. I'm an equal opportunity questioner. We'll start with Dr. O'Brien.

So I was very struck by that estimate, the dual use estimate, 92.8%. That's starkly different than the 50% that we were provided earlier. And so I just would like to clarify what the source of that is. Obviously, a high dual use rate is concerning, particularly considering the conclusion from the clinical data that showed that there was -- fewer would actually switch coupled with the epidemiologic data that shows comparable relative risks for the dual users versus the exclusive cigarette smokers. So that being said, what's the source of that 92.8% and what's your denominator on that? Just

to give us some context for how many people we're talking about.

DR. COLEMAN: Sure. So the source of information, that's from the Applicant's NTBM study. So they looked at -- so the denominator they provided there was a weighted sample of Camel Snus users in their study. So they were able to ascertain brand information for past 30-day users, so this is among Camel Snus past 30-day users. They provided a breakdown, which is presented in our briefing materials, of different combinations of dual and poly use.

So, in totality, it's sort of any different combination of dual/poly use among Camel Snus users total about 90 -- roughly 93%. So there was roughly 7% that were exclusive Camel Snus users. So that's the source of data for that information.

DR. KING: Okay, got it. Thank you. And I would also like to reinforce this youth issue and I've said this before at previous meetings, so it should be no surprise that it's coming out of my mouthpiece, but I think that when we look at the broader population impact, it's critical that we look at initiation among youth and, you know, that ultimately helps you to identify what is going to be that benefit or harm of what is being proposed to be done here.

So that being said, you know, I think that it's very concerning that we don't have any data among kids to make an informed decision. And so I'm wondering, particularly from the FDA folks, do we not have data from PATH that would enable us to at least get at snus with more specificity than maybe we couldn't with NYTS, or even a brand descriptor question or something to get us at what is the prevalence of use of snus in general and possibly even this particular product among youth, because I suspect that the Applicant does not collect any data among youth.

DR. KITTNER: That is something we'll have to get back to you on, I can't answer that right now.

DR. KING: Okay, wonderful. And then the last question. So I was also struck by the marked availability of flavors of these products. It's interesting to me that many of them are concept flavors, that seems to be an approach that's being taken a lot more recently, particularly as several communities and other entities are addressing characterizing flavors. The majority of these flavors appear to be concept flavors.

That being said, on Slide 29 on page 3 of our documents there was this overview of differences in product design as well as, you know, some similarities, but I was struck that

there was no assessment of the differences in formulation, just the similarities and formulations.

And so I'm interested, based on your review outside from, obviously, the weight differences of these 600 mg versus 1,000 mg, is there any variability in the formulation of these products, particularly across flavors, that would lead us to believe that there would be any variation in either (a) clinical outcomes or (b) epidemiologic outcomes?

And the reason I say that is because many of the studies that were presented here didn't appear to be conducted across all six and there were some instances where certain flavors were included and particularly, the variation in NNN levels were a little bit concerning to me.

And so I'm wondering if there is variability in terms of formulation outside of just those flavors that maybe we should know about so that we can make a fully informed conclusion about these clinical endpoints as well as some of the other epidemiologic data that's been presented to us. And if it's more appropriately directed towards the Applicant, I'd be interested in anyone's thoughts who has some intel on this. Thank you.

DR. KITTNER: The Applicant may be in a better situation

to answer that.

DR. KING: Okay. So I don't know if the opportunity is now or later that --

DR. MERMELSTEIN: I'll ask Dr. Shiffman if there's relevant data.

DR. SHIFFMAN: Yeah, so with regard to the formulations, I'll ask Dr. Borgerding to address that since he's much more of an expert on that than I am.

DR. BORGERDING: All six styles of Camel Snus use the same low toxicant blend of tobaccos. They all have the same specifications as far as pH and the same types of materials and so on as far as fleece. The only difference amongst the styles is the flavor and also the two sizes of pouch. So they would all be the same. It's a very simple product, as you saw from Dr. Ogden's overview, in terms of tobacco in a fleece pouch and certain heat treatment and then the flavor added and some sweetener and so on.

In terms of your question about biomarkers, we don't see a difference in terms of the kinds of reductions we're seeing based on two quite different flavors, for example. If I could have the --

DR. MERMELSTEIN: Well, I think we'll hold off on the

slides for now. Thank you.

DR. BORGERDING: At some point, if it's useful, we have that information and again, the types of reductions we see when people switch completely, for example, in confinement, we would see reductions in NNN for both types of flavors.

DR. KING: So how about across all six of the flavors, not just the two that were assessed? So your expert opinion is that we would see those same clinical endpoints regardless of the six different products, not just the two that were assessed in those particular studies?

DR. BORGERDING: Yes.

DR. KING: I just want to be clear.

DR. BORGERDING: We provided information in the application about different pouch sizes, about all the various styles, and we expect the same types of reductions.

DR. KING: Okay.

DR. MERMELSTEIN: Great. Thank you, Dr. King. Okay, on the phone, Dr. Kozlowski.

DR. KOZLOWSKI: Thank you. It looks like the chemistry is not looking more harmful than the chemistry of smokeless tobacco products a few decades ago and the toxicology also looks like it's not more problematic than the smokeless tobacco

products on the market a few days ago. And some people would be inclined to think of the epidemiology as kind of providing more of a bottom line about what the consequences of some of these chemicals and toxins would be.

So what's your feeling about the -- do you have reason, based on the chemistry differences, the toxicology differences, to discount the importance of the major Henley CPS studies indicating an all-cause mortality of 1.18 based on the hazard ratio? Do you think that might provide a kind of upper limit for this, for the risks of the snus products?

In some sense I'm asking do you consider one type of information somewhat more relevant to the policy issues, the chemistry, the toxicology and then the epidemiology, and is there a reason to discount what we know from the CPS studies?

MS. COREY: Yeah, I think -- this is Cate Corey, I presented on the epi evidence and I think we feel like the Henley evidence from CPS-II, you know, provides a reasonable characterization, as far as we're aware, of risks posed by smokeless tobacco products, but there may be other information that the other disciplines want to add to that.

DR. MERMELSTEIN: Hold on, they're just conferring to answer your question.

DR. KOZLOWSKI: Thank you.

DR. KITTNER: So I think that's one of the things that we're asking the Committee to help us with in terms of balancing the lines of evidence from the various disciplines. So I think that will unfold over the next day and a half for us to sort of hear what your thoughts are in terms of assessing that information.

DR. MERMELSTEIN: Great, thank you.

Okay, Dr. Thrasher.

DR. THRASHER: Yes, thanks. So this question is for either Dr. Young or Dr. Corey. The toxicological and clinical biomarkers focus on the shortened list of HPHCs, of which there are nine. Is there any reason for us to be thinking that there might be some other important HPHCs that are kind of more relevant for snus compared to other smokeless tobacco products, or should we feel reasonably confident that that shortened list of nine really capture the primary constituents that we should be considering in this evaluation?

DR. CARBONARO: Theresa Carbonaro, a pharmacologist at CTP. In terms of the biomarker data, that was all that was submitted by the Applicant in terms of the TSNAs. There is a number of other biomarkers that may be relevant but are really

limited, based on the limitations that were described in our presentation, on how much we can really rely on that information. And I think chemistry might have more to comment on that.

DR. YOUNG: Hi, this is Mimy, chemistry. We evaluated the nine HPHCs in the abbreviated HPHC list and it does capture representative HPHCs in regards to the toxicity of the Camel Snus products.

DR. MERMELSTEIN: Thank you.

Dr. McKinney.

DR. McKINNEY: Yeah, as I think about the risk assessment equation, exposure and the hazard, we heard a lot about the hazard and the chemistry and as I was looking at the chemistry results, specifically for snus and cigarettes, I had a tendency to multiply those numbers by potential exposure because the data was expressed on a unit of pouch and a unit of cigarette. So the chemistry results for the cigarettes, I think, I multiplied by 15 and then for the snus I may have multiplied by 2.2 or something like that, but I could be a little off with that number, and I came up with a potential comparable exposure.

Did the toxicologists talk about that and did you guys

consider that in your assessment? Or lower exposure, for that matter. Of course, the biomarkers showed something, but --

DR. AHMED: So this is Kausar Riaz Ahmed, toxicology. Dr. McKinney, so we were able to get exposure data from what is available in the literature, but I don't think the Applicant gave us sufficient information that allows us to adequately capture the exposure that we usually get from Camel Snus products. So we weren't able to make that evaluation.

DR. MERMELSTEIN: So can I ask a clarifying question? So is your question more getting at what might be a daily exposure based on those rates, that if someone's smoking 15 cigarettes a day and you multiplied compared to, say, four pouches a day and multiplying?

DR. McKINNEY: I think that's exactly right, it's a calculation and the numbers may come out and match with the actual data from the biomarkers, but that's my question.

DR. AHMED: Right. And to answer your question, like I said before, there is information available from different publications, somewhat, and users' usual exposure could be to a smokeless tobacco product, pouched versus non-pouched smokeless tobacco product, but I do not think, based on information that was given to us, there was sufficient information that allowed

us to make those calculations.

DR. MERMELSTEIN: On the phone, Sally Herndon.

MS. HERNDON: Hi. This is a question about the uncertain data on the relationship of diabetes risk. I know in the 2014 Surgeon General's report one of the new risk factors for cigarette smoking was that it's associated with diabetes and I wondered if there are additional studies in the works that clarify the relationship of smokeless tobacco products to diabetes risk which also, of course, is a major risk factor for cardiovascular disease.

MS. COREY: Hi, this is Cate Corey, epi. We're not aware, currently, of any unpublished or forthcoming data around the relationship between diabetes and tobacco use.

DR. MERMELSTEIN: Dr. Weitzman.

DR. WEITZMAN: I do believe that there is -- there are a number of studies that relate smoking, both active and secondhand smoke exposure, to the metabolic syndrome, one component of which is diabetes. I think there's fairly substantial literature on that.

DR. MERMELSTEIN: Go ahead.

DR. OSSIP: On Slide 20, getting back to the 5-day assessment of biomarkers of exposure, a question is, is that a

reasonable time frame? Is it the right length of time for measurement or is it possible there would be some changes were use of snus measured for a longer period of time?

So we saw some data earlier that people tend to increase their use of snus as they become more accustomed to the product and in this case, it was exclusive use. And so with exclusive use, would one -- might one expect to see that same sort of a pattern where a measure of exposure, biomarker of exposure measure, might underestimate or, I guess, potentially overestimate what the exposure would be with a stable pattern of snus use?

DR. CARBONARO: Theresa Carbonaro again, pharmacologist. So I think my understanding is that it is an okay time period for smoke-related ones, if you decrease smoking, like the measurements of acrolein or other smoke -- like the actual biomarkers from smoke may decrease in that period, but it's not long enough for all of the biomarkers to decrease or to expect a decrease in that amount of time.

It is also a caveat -- that the use in that study of Camel Snus products was less than would be -- may be expected in natural settings. So there is that caveat as well.

DR. OSSIP: Thank you.

DR. MERMELSTEIN: Dr. Wanke.

DR. WANKE: So I have a question about the modeling studies that were presented by the Applicant. The FDA didn't provide an overview of the modeling data that was presented and so I was wondering if you had done an independent assessment of that research, and particularly looking at the assumptions and the inputs and whether there was accuracy in that data, particularly given the discrepancy that we're seeing in the dual use patterns.

It sounds to me like the Applicant used a 0.6% use rate, which is comparable to the 0.5% current use rate, although that's just trying within the past 30 days, it isn't necessarily consistent use, but it sounds like there's -- the discrepancy may really lie with the 50%, I think, if I'm understanding it correctly, that the Applicant said that they presumed a 50% exclusive rate but again, with variation over time, with potentially some continued switching back to smoking, but it would really be more like a 7.2% complete switching rate. And so I'm curious about FDA's assessment of the modeling data.

DR. KITTNER: We are still evaluating the modeling, so at this point we're not able to comment. Oh, sorry. You're going

to make a comment, okay.

DR. TEKA: So the -- oh, sorry. My name is Dr. Wondimu Teka from statistics branch, ad user modeling part. So the -- these based on the likelihood of use study, then using the predictive algorithm. Then, based on that study, the switching probability, the switching probability based on age category is from 60 point -- 66.5%, so 1.7%, for example, for Execution 1. The 66.5% is for age category 13 to 17. The 1.5% is for the age category from 67 to 72 -- so this is switching, completely switching is 50% of this. That is based on assumption. The -- of smoking is 50% of switching, which is predicted within the predictive algorithm. So completely switching on the modeling is about 8.2 for the age category from 13 years to 17 years.

DR. WANKE: So let me clarify, then. So let me make sure that I'm understanding correctly. So you're saying that they did use a 50% complete switching rate?

DR. TEKA: Yes.

DR. WANKE: At least for some age categories.

DR. TEKA: Yes.

DR. WANKE: If not most age categories?

DR. TEKA: Pardon me?

DR. WANKE: Did they have different rates?

DR. TEKA: Yes.

DR. WANKE: Did they presume different inputs --

DR. TEKA: Yes, yes.

DR. WANKE: -- across age categories?

DR. TEKA: So yes. So switching probability predicted from the -- using the algorithm from the likelihood of use study is based on age category.

DR. WANKE: Okay.

DR. TEKA: From 13 to 17, 18 to 22, 23 to 27 and so on. So the switching decreases along those age categories. And the maximum for Execution 1 is 60.5. The minimum is 1.7. Complete switching --

DR. WANKE: The minimum switching rate?

DR. TEKA: What did you say?

DR. WANKE: The minimum switching rate is 1.7?

DR. TEKA: The minimum switching rate is 1.7%, that is for all age group above 68 years old.

DR. WANKE: Okay. Okay, I see what you're saying.

DR. TEKA: So completely -- yeah, completely switching is 50% of this. That is based on the assumption, on the modeling part.

DR. WANKE: Okay, so it sounds -- it still sounds like it's different than what the data is showing for complete switching rates, as far as the model is -- has a much more optimistic rate of complete switching across age groups than what we're seeing for complete switching in survey data. Thank you, I appreciate it.

DR. MERMELSTEIN: On the phone, Dr. Giovino.

DR. GIOVINO: Hello, yes. I have a procedural question for the FDA or at least a question about another process. The proposed rule limiting NNN to 1 µg/g, what's the status of that and should the Committee be factoring that into its thinking at all?

MR. ZELLER: Gary, this is Mitch, I'll answer that. The Committee should not factor that into its thinking at this point. The comment period closed and it remains a policy under consideration as the comments are being reviewed. I think the Committee's task is challenging enough. I think trying to account for what might or might not happen in an unrelated rulemaking would further complicate your work.

DR. GIOVINO: Okay. Thanks, Mitch.

DR. MERMELSTEIN: Dr. Bierut.

DR. BIERUT: Can I also ask a clarifying question, which

is -- has to do with the landscape of smoking behaviors in the United States are dramatically changing with products other than combustible cigarettes and I don't -- when I see smoking, I don't know what that means at times and I think, especially if I was 18 years old or 20 years old, I might have a different thought on that. And so is there any guidance that you could give us?

DR. HOLMAN: I would say that point should come out in a discussion and as it impacts or affects how you vote and you should provide that sort of information to us.

DR. MERMELSTEIN: Other questions from the Committee? Dr. Wackowski.

DR. WACKOWSKI: One quick question. So if these proposed ads are approved, the order is given, can the company continue to have other Camel Snus ads that do not have these claims such as ads that they might have now, such that these ads would coexist with sort of the status quo ads? Or is this order a replacement of existing ads? Does that make sense?

DR. HOLMAN: So I guess, again, I'll say what I said about an earlier question this morning which is, that that's the sort of question we'll have to answer if we get to the point that we decide we're going to issue marketing orders for modified risk,

that would be one issue that we'd have to deal with at that time. But again, it's kind of premature at this point to try to answer that question.

MR. ZELLER: I guess what I would add to that is for ads that arguably don't contain any modified risk claims or information, in the hypothetical future world where we were to authorize a claim, to the degree that you want to speculate about what the world would look like, while the company gets to decide other types of advertising that they want to engage in that don't cross the MRTP line, it is conceivable that there could be non-MRTP advertising, more lifestyle advertising or something else that would not cross that MRTP line, because they can do that.

And it's as much a question for the company, you might want to put the question to the company, if you'd like, as it is to speculate what the future world would look like.

DR. MERMELSTEIN: Other questions from Committee members to the FDA?

DR. GIOVINO: I have one, if I may.

DR. MERMELSTEIN: Go ahead, Gary.

DR. GIOVINO: I know there is a built-in system of postmarketing surveillance because I work -- have worked on

that since the 2001 IOM report, in a way. But if an order were to go through, does FDA have methods other than those large surveys to assess if the company is deviating from things that influence the public health norm? I guess I'm thinking of the Supreme Court definition of pornography and the justice said I know it when I see it, or some justice said that. And you know, will you be able to just do to qualitative assessments of marketing and say wait a second, does this -- you know, help me understand the scenario after. I mean, I know about the surveys, but are there other qualitative things that you all can do when a company shows marketing to you? Or public statements.

MR. ZELLER: This is Mitch, Gary. It's a fair question and it's hard to answer with specificity, other than to say we have certain ways. Were there to be a marketing authorization, there would be certain commitments that the Sponsor would have to make. You heard the company allude to that at a couple of points this morning in their presentation.

As for our ability, I'll just answer very generally and say yes, we have -- we have ways of assessing what is going on in the marketplace and we are not the only agent looking. From time to time there are third parties who bring information to

our attention if they believe that a line has been crossed that requires us to investigate. And I'm speaking vaguely because we don't generally talk publicly about our methods that would exist in parallel in -- were there to be a marketing authorization to any mandatory postmarketing commitments that the company would agree to do.

DR. GIOVINO: That helps. Thank you, Mitch.

DR. MERMELSTEIN: Dr. Wanke.

DR. WANKE: Since we're talking about hypotheticals of what FDA can and can't do, I'm struck by the fact that, for the MRTP applications, it is the Applicant that is bringing forward their statements and unlike, say, a graphic health warning where FDA can recommend or, you know, determines what those are, I'm wondering if FDA can recommend changes to the wording or if it really is the case that what the Applicant presents is an all or none. It's either yes or no the way it's worded, but is there an opportunity to say something like less risk, you specify less risk can only be said when you say less risk as compared to smoking?

DR. KITTNER: Yes, we can have labeling negotiations or give input in terms of what kind of language we think will be best for the product.

DR. WANKE: Thank you.

DR. MERMELSTEIN: Last round for the Committee to the FDA. Anyone on the phone have another question to the FDA?

MS. HERNDON: Yes. This is Sally Herndon. Following up on that, my question is process for understanding the reach of such a campaign and regulatory approaches to ensuring that message is met for current smokers are being received by current smokers and not by young people.

MR. ZELLER: Sally, this is Mitch. I'll start and then I'm going to ask colleagues from the Office of Science to add on.

I think that, generally, were there to be a marketing authorization, those are precisely the kinds of unintended consequences that we would all be looking for in the field. It's why, in its wisdom, Congress said, as you heard this morning, that were there to be an MRTP claim authorized, they are time limited for a maximum of 5 years.

And as you heard the Sponsor say this morning, FDA can withdraw the authorization if it feels that it has grounds to do so. And that's all on the basis of what would be detected postmarketing and goes to the heart of why, even with an authorization, they are time limited and the company would have

to come back and reapply to get a renewal or an extension.

MS. HERNDON: Thanks, Mitch.

DR. MERMELSTEIN: Okay. Well, I want to thank our presenters from both RJR and from the FDA. And, Dr. Shiffman, that you were jumping up and down, one last quick comment.

DR. SHIFFMAN: A question for you. I think there were some more areas of fact that weren't completely or correctly addressed. The question is, I know in the past, applicants have come back on the morning of the second day to address that. We seem to be running out of questions and there's still some time, so I was going to offer the opportunity, if you and the Committee wish, to have that discussion now or wait until tomorrow morning.

DR. MERMELSTEIN: I think I'm going to pose it back to the Committee to see whether the Committee had some need for clarifying questions.

MR. ZELLER: From the FDA perspective, we would be willing to offer up 15 minutes now, but the Committee -- the members of the Committee should opine as well, it's really your time.

DR. MERMELSTEIN: Go ahead.

UNIDENTIFIED SPEAKER: I've lost you.

DR. MERMELSTEIN: Yes. That was a yes, go ahead.

DR. SHIFFMAN: That was a yes.

DR. MERMELSTEIN: Grab your time while you've got it.

DR. SHIFFMAN: Okay, here we go. So there were several issues -- there were several, so I'm hoping we can address them correctly. One of them was a distinction that maybe got lost between the chemistry, what's in the product and what actually comes out and results in an exposure to a human being using the product, and I will ask Dr. Borgerding to be incredibly efficient in answering that question.

DR. BORGERDING: Yes, we heard from earlier speakers about much larger amounts of certain things in a pouch of snus as compared to cigarette smoke. And in fact, in one of the slides we saw earlier for NNN, all snus, be it from Sweden or in the U.S., or smokeless products, were higher than cigarette smoke.

But as was also indicated by several speakers and in some of the briefing materials, of course, they're quite different products, how they're used is quite different. Cigarettes are burned to produce smoke. Snus is used by placing it in the mouth and then, importantly, removing it after use. So much of what's in the pouch remains there after use. If I could have Slide 2, please. Just as a reminder, we saw earlier that the nicotine content in a pouch is much higher than it is in

cigarette smoke and yet the exposure to nicotine is slightly reduced compared to cigarette smoking. That's something that we see for other compounds as well. It would be true for NNN. If I could have Slide 3, please.

So, again, the amount of material in the pouch is much greater than in machine-generated cigarette smoke. Actual exposure, both natural adopters and switchers -- and I would point out that we've done studies with smokers over the week time course, specifically reducing them from 20 to 10 to 5 or 0 and we know, with the exception of NNK, these biomarkers do change in that time course. NNK can change partially but not completely in that time course.

But again, here, the point is while there's much more in the pouch, the exposure is actually reduced. In terms of arsenic and cadmium, it's the same type of result. The reason that it's so is that these things are not particularly soluble, they're not removed from the pouch during use. If I could have Slide 3, please. This is now biomarker data looking at cigarette smokers, smokeless tobacco users in the middle, middle column, and nonusers of tobacco in the right-hand column and what we see is that there's no difference between smokeless tobacco users and nonusers in terms of their exposure to

arsenic. There would be a similar result for cadmium. In the interest of time I won't ask for that to be called up.

To put that in context, if I could see Slide 2, please, this looks at the amount of arsenic that's in a pouch of snus as compared to other smokeless tobacco products, the ones that were used as part of the NHANES study and looked at the -- or produced the biomarker data that we just saw. And what we see is that Camel Snus is on the low end of what we would find for products in the U.S., ones that produce no difference in biomarker response than nonusers of tobacco.

So, again, the key message is what's in the pouch isn't a measure of exposure. Biomarkers do provide us with the measure of exposure.

DR. SHIFFMAN: Whether that it was efficient to get other data as well. I want to make an important -- I guess it's an addition. I can't remember if it was Dr. Ossip or Dr. Wanke who asked whether there were data on younger populations and exposure to modified risk messaging. It was Dr. Wanke. And in fact, there is a study published recently by Al-Turki (ph.) involving an explicitly adolescent sample and an adult sample. They exposed that to -- they had a control group that got similar sort of messages or actually didn't see anything about

risk, and a group that got a reduced exposure message. They included snus among those products, but they actually tested other products and found no difference, so they report their data in aggregate.

And one thing showed -- if I can see Slide 1. This is their likelihood of use measured, they used a variant of the susceptibility measure and what you see is, as we saw in our data and as FDA indicated and we see in many published studies, adults do increase their interest in a product if it has low risk. They saw no difference among the adolescents. And so there is data to indicate that adolescents do not respond to modified risk messages and that's consistent with the data we showed you -- we showed you for young adults as well.

One other point has to do with the potential for switching and there are several studies which were reviewed in an FDA review paper, it wasn't a meta-analysis but a review paper that used longitudinal data to look at transition probabilities and in a moment I'll be able to show those. So if I can have Slide 2. To be clear, the 1-year and 4-year studies are two different studies, so that's the longitudinal follow-up over 4 years.

So Shu-Hong Zhu's study was over 1 year and the later

study was over 4 and these are the probabilities that a person transitions from smoking to exclusive use of smokeless tobacco. So you can see that the probabilities are up into the double digits by the time you get to 4 years.

And, importantly, as I referred to earlier, it's much more common that it goes to dual use. The dual use leads to exclusive use and actually the probability of going from dual use to exclusive use is high and the probability of going from dual use to exclusive smoking is lower. So there is already switching going on in the population.

And I want you to remember that that's where -- for switching. Why would you switch if you believe that the products are just as harmful and perhaps, as we've said, not as satisfying? So the whole point of the -- process is giving smokers accurate information in order to motivate them to switch, even if the product is not quite like their old familiar cigarette. And so it's important to think about what we're talking about, which is giving people a motivate to switch and we're also talking about the risk relative to smoking. We saw a lot of absolute risk values put up and I don't think everyone in this room, including folks on this side of the table, are saying that snus has no risk.

That isn't the point and indeed, that's why we went to the trouble to show that people who are out there using tobacco don't increase interest when we tell them about reduced risk. The point is to get smokers who have this very high risk to make the transition to a less risky product. So it's the relative risk that really matters, as well as looking at exposures rather than content of products. And I think we're within our time frame, I hope.

DR. MERMELSTEIN: Yes, but we do have one other question from Dr. Kittner.

DR. KITTNER: Hi. I have a question. Actually if the 15 minutes is over -- because I actually was hoping that the Committee Chair would consider asking if Dr. Stepanov might be able to share some information to alleviate concerns that folks were having around uptake amongst youth perceptions and modeling youth in terms of smokeless tobacco. So while we have her here today, I was wondering if she might be able to share her perspective on smokeless tobacco in youth. If not, that's fine, but I just wanted to give you the opportunity while you're here today.

DR. STEPANOV: I got up just to answer your question to me, that I don't really have this kind of data.

(Laughter.)

DR. STEPANOV: My expertise is in toxicology and chemistry of products and I conduct studies that involve some of these elements but wouldn't have enough background to comment.

DR. KITTNER: Thank you.

DR. MERMELSTEIN: Thank you.

We do have one other question from Dr. Thrasher on the phone, so you're still within your few minutes.

DR. SHIFFMAN: Okay.

DR. MERMELSTEIN: Stand up there, Saul.

DR. THRASHER: All right, thank you for your patience. I guess one of the questions that I have is with regard to the consumer perception studies, so Saul, you may be best to respond to this. I do wonder about responses to the harm reduction messages in the context of the warning labels, which were kind of randomly rotated across the different executions. Maybe what concerns me the most is the possibility of sending conflicting information to consumers, information potentially interpreted as conflicting around the mouth cancer, in particular, and I'm wondering did you find any differences in the impact of the harm reduction messages across the warning label conditions?

You didn't present that information, but my assumption is that you could generate greater confusion and alter people's perceptions of risk when the harm reduction messages are presented in the context of something like mouth cancer when you're also talking about reducing the risk of oral cancer.

DR. SHIFFMAN: So your question is about the -- in a sense, the interaction between the warnings, which give an absolute risk statement, and the modified risk statements, which present data on modified risk.

And the short answer is that when people see the absolute risk warning in the absence of the modified risk statement, they're actually less informed and their estimate of the risk, the relative risk, is that smokeless -- well, snus, in this case, has a higher risk than smoking. That's what you see in that condition. When they see that modified risk information, when they see the warning and the modified risk information -- I'll show you that in Slide 2, please. So actually we have a better slide, but we'll go with this one.

The complication here is that beside the mouth cancer warning there's a gum disease and oral disease warning, which people also interpret as mouth cancer, so that's in the control here in the blue bar, if you will.

But what you see is that in the presence of the warning, people do understand that when given a modified risk statement, that it's not a risk and if we can show the data, please, if you contrast the -- specifically, the mouth cancer warning to the warnings that are less about mouth disease -- no tobacco product is safe and so on.

What you see there is that in the absence of the modified risk information, people come to believe that smoking causes more oral cancer than smokeless tobacco or snus, which is not the case. And in fact, part of the reason that happens is that when people are exposed to the modified risk message -- yes, let's see, please, Slide 3. So these are the data on the left when people saw the mouth cancer warning and they either did, in the yellow bars, or did not see the modified risk statement about oral cancer and what you see is if you see the warning and you don't see the modified risk statement, you'll believe that smoking -- that snus, actually, carries more risk than smoking, which is clearly not the case according to the epidemiology.

If they saw other warnings unrelated to oral disease, so either the mouth cancer or oral disease warning, you see that they reacted to the modified risk information. Those who saw

the modified risk information give you a lower estimate of the risk relative to smoking.

Another important thing, though, is that that -- perception comes partly not just from a change in the perception of snus, but a change in the perception of risk of smoking. I'm sure they don't go through this cognitive logic explicitly, but think about what it tells you if you have a product that says this can cause oral cancer, but by the way, less so than smoking, that will teach you that smoking has a very high risk of oral cancer, which is true. So people actually make a reasonable inference and come to believe, given the presence of a mouth cancer warning, that this has less risk, again, but not no risk. And in the absence of a modified risk statement, the warnings actually lead to misperceptions. That was a long answer to a short question. Jim, did I address your question?

DR. THRASHER: Yeah, I believe so. I'll follow up tomorrow, if necessary.

DR. SHIFFMAN: Okay. And you'll see this in the literature soon enough.

DR. MERMELSTEIN: Great. Thank you very much. Again, thank you both for all the presentations today and the strength

of discussion.

Given the time, I'm wondering if we might want to just have some concluding comments for the day to get the Committee ready for tomorrow's discussion, and I don't know, Dr. Kittner, if you wanted to wrap up or no, or want me to.

(Off microphone response.)

DR. MERMELSTEIN: All right. So, you know, I think that tomorrow what we're going to end up doing is we'll hear some more public comments and have an engaged and good Committee discussion. And I think that for the Committee, what we're going to have each of you do tonight is reflect back on what we've heard today. I think there are some critical distinctions to help keep in mind and so I'll just give some quick bullet points and please correct me at any point. And these are in no particular order, but I do think that, again, this is about modified risk and to keep that frame in mind, which is different from absolute risk. So that's one important consideration.

I think we need to think about targeted audiences and who these reach and what the intended things are and what those implications may be.

I think it was very helpful hearing the clarifying

comments because I do think the Committee was understanding the difference between what's in the product versus how it's used.

And that troubling table that many people saw that showed high levels of constituents and what actually -- how that relates to exposure is important for everybody to grapple with and get comfortable on what's the difference between what's in a product versus what's in the exposure in the biomarker and to think about that so that we're all comfortable with some of the essence of the questions and what it means as things are actually used.

And to consider, as well, what we might know about patterns of use and what data we have and what data we don't have in terms of -- we have a lot of questions now because we're smarter than we were a couple of decades ago when surveys were -- you know, were fielded. So none of the data are perfect, but I think that's what we have to discuss is what we might know about likely patterns of use and the dynamic nature of behavior and how that plays out in terms of the modeling and our estimates of likelihood.

So a lot for us to each think about tonight, but you have to think solely, you cannot think in consultation with any other Committee member or other people. So, again, the

Committee test is for you to go home and have a relaxing evening but don't talk to others about this.

So we will start again tomorrow morning promptly at 8:00?

UNIDENTIFIED SPEAKER: Yeah, 8:00 a.m.

DR. MERMELSTEIN: Because many of us want to get out and home tomorrow, so we're going to have an accelerated day tomorrow and starting at 8:00. So thank you all for your participation and attention. Thank you.

(Whereupon, at 5:00 p.m., the meeting was continued, to resume the next day, Friday, September 14, 2018, at 8:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

September 13, 2018

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Tobacco Products.

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